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Stereocontrolled Synthesis of Polyfunctionalized *cis*-Decalins from 2-Methoxyphenols: Total Syntheses of (±)-Eremopetasidione, (±)-3*β*-Angeloyloxyfuranoeremophilane, and (±)-3*β*-Methacryloyloxyfuranoeremophilane

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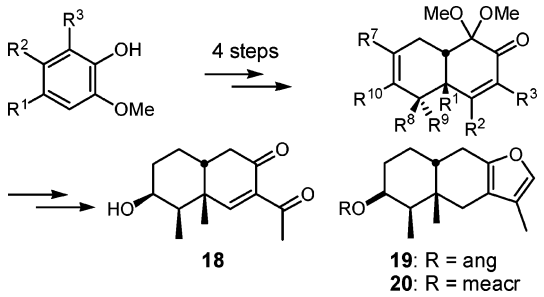

A four-step stereocontrolled synthesis of polyfunctionalized *cis*-decalins is described, involving oxidation of 2-methoxyphenol, intermolecular Diels−Alder reaction, olefination, and Cope rearrangement. Application of this efficient strategy to the total syntheses of (±)-eremopetasidione, (±)-3*β*-angeloyloxyfuranoeremophilane, and (±)-3*β*-methacryloyloxyfuranoeremophilane was accomplished from creosol and ethyl vinyl ketone via a common intermediate **21**.

Introduction

The decalin ring system is found in a wide variety of terpenoid and steroid natural products[1−3] with a wide-range of biological activities.[2,3] Owing to their importance in nature, the synthesis of decalins has become a major focal point of synthetic chemistry. The structural complexity of the isolated natural products demands the development of new and efficient strategies to construct stereochemically rich and multifunctional decalins. For this reason, there has been a great deal of interest in developing a multitude of methods for their synthesis, as reflected by the flurry of recent reports in this area by various groups.[4,5]

Recently, we have demonstrated that masked *o*-benzoquinones (MOBs) are valuable intermediates in organic synthesis.[6] Among these, we have developed several strategies to construct the *cis*-decalin skeleton[7,8] and applied these methodologies to the total synthesis of several natural products.[9] One of these approaches is from an intermolecular Diels−Alder reaction of

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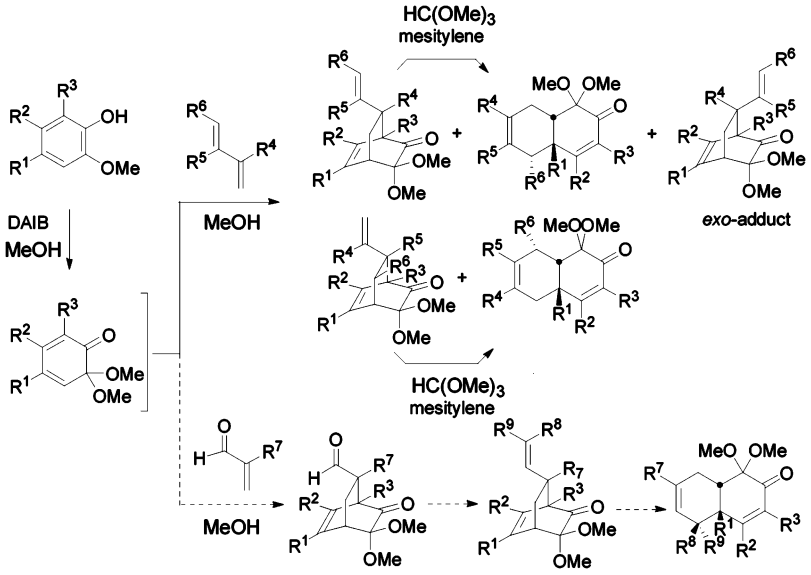
SCHEME 1



MOBs with unactivated acyclic dienes to provide bicyclo[2.2.2]-octenones along with *cis*-decalins (Scheme 1).[8c] In some cases, *exo*-adducts were also obtained. When an unsymmetrical acyclic diene such as isoprene was used, the resulting mixture of bicyclo[2.2.2]octenones and *cis*-decalins was difficult to separate. From a synthetic point of view, a useful synthetic step must provide a single product in high yield. This prompts us to develop an alternative route to construct *cis*-decalins. In our previous studies,[10,11] the intermolecular Diels−Alder reaction of MOBs with various dienophiles such as methyl acrylate, methyl methacrylate, and methyl vinyl ketone proceeded in a highly regio- and stereoselective manner to furnish a single cycloadduct. Accordingly, if α,*β*-unsaturated aldehydes are chosen as dienophiles, we should generate a single cycloadduct in each case. The transformation of the aldehyde groups of the cycloadducts into olefins followed by Cope rearrangement would be expected to furnish the *cis*-decalin skeleton. We now report a four-step stereocontrolled synthesis of polyfunctionalized *cis*-decalins via sequential oxidation of 2-methoxyphenols, intermolecular Diels−Alder reaction of MOBs with α,*β*-unsaturated aldehydes, olefination and Cope rearrangement. This new strategy will only produce one main product in each synthetic step.

Results and Discussion

(a) Intermolecular Diels−Alder Reactions. The intermolecular Diels−Alder reactions of MOBs **2a**−**e** generated from the 2-methoxyphenols **1a**−**e** in the presence of acrolein and methacrolein, respectively, as outlined in Scheme 2, were first examined, and the results are summarized in Table 1.

At the outset, when the reaction between acrolein and MOB generated from creosol (2-methoxy-4-methylphenol, **1a**) was carried out under the usual conditions,[10] the yield of formylbiyclo[2.2.2]octenone **3a** was very low and unoxidized creosol always remained. We attributed this to a side reaction between diacetoxyiodobenzene (DAIB) with acrolein. Then, instead of adding creosol to the mixture of DAIB and acrolein, we added DAIB in methanol to the mixture of creosol and acrolein in methanol using a syringe pump at room temperature over 4 h. The reaction mixture was stirred for another 8 h followed by the usual workup and chromatography to provide bicyclo[2.2.2]octenone **3a** in 85% yield. In the same way, the MOBs **2b**−**e** were generated in situ by the DAIB-mediated oxidation of 2-methoxyphenols **1b**−**e** in the presence of acrolein and methacrolein, respectively, to produce the expected products **3b**−**d** and **4a**−**e** in good yield. The only exception was the MOB **2d** and methacrolein, which gave an unsatisfactory conversion to **4d**. The yield of the cycloadduct **4d** was substantially lower, presumably due to the steric hindrance caused by the additional methyl group in the dienophile and the MOB **2d** easily underwent self-dimerization. Unfortunately, attempts to improve the yield by using a high dilution technique, a large excess of methacrolein, slow addition of DAIB or refluxing conditions were unsuccessful.

The structures of all the new compounds were established on the basis of their IR, ^{1}H and ^{13}C NMR, DEPT, and low- and high-resolution mass spectral analyses. For most of the adducts in both low-resolution and high-resolution mass spectra recorded in electron impact mode (70 eV), the peaks corresponding to the molecular ion (M^+) could not be detected; instead, the peaks corresponding to $M^+ - 28$ were observed, indicating the facile extrusion of CO from the molecular ions. This observed phenomena has literature precedents.[10,11]

The regio- and stereochemistry of all the isolated bicyclo-[2.2.2]octenones **3**−**4** are in line with the literature precedents.[10,11] The *endo*-stereochemistry of the aforementioned bicyclo[2.2.2]octenones was further proved by chemical correlation through their ability to undergo the Cope rearrangement or by comparison with known compounds after olefination.

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SCHEME 2

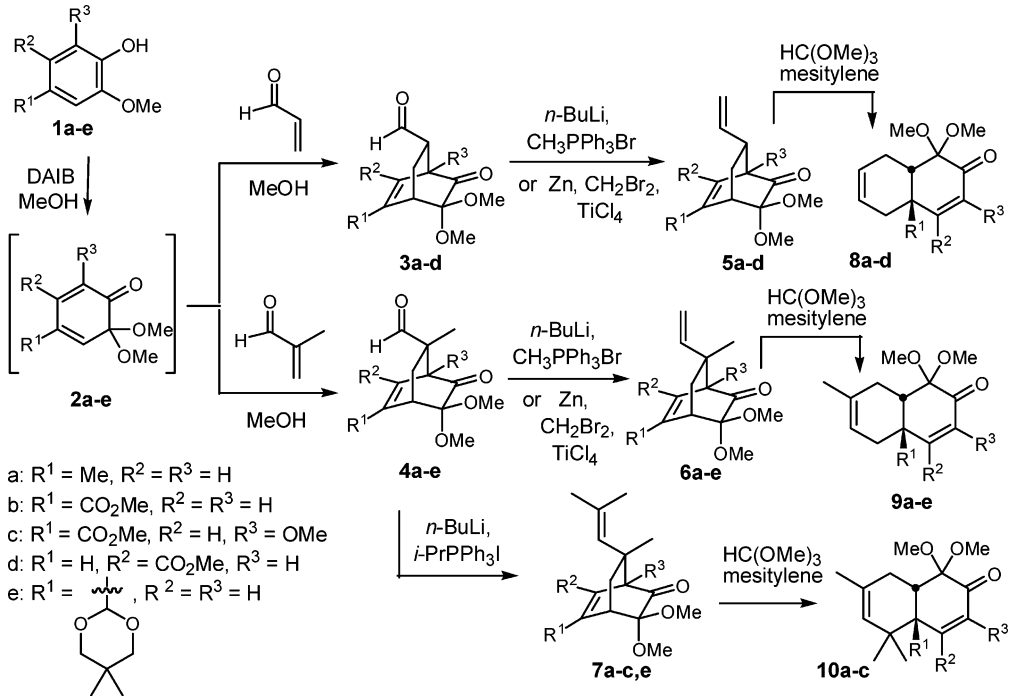

TABLE 1. Intermolecular Diles-Alder Reactions of Masked *o*-Benzoquinones 2 with Acrolein and Methacrolein and Olefination of Cycloadducts 5−7

				Diels-Alder reaction			olefination		
entry	phenol	dienophile	MOB	addition time/ temp [°C]	after addition	adduct/ yield(%)	*n*-BuLi, CH_3PPh_3Br	Zn, CH_2Br_2, $TiCl_4$	*n*-BuLi, *i*-$PrPPh_3I$
1	**1a**	acrolein	**2a**	4 h/rt	8 h	**3a**/85	**5a**/65	**5a**/88	−
2	**1b**		**2b**	4 h/rt	8 h	**3b**/80	**5b**/50	**5b**/80	−
3	**1c**		**2c**	4 h/rt	8 h	**3c**/87	**5c**/45	**5c**/88	−
4	**1d**		**2d**	4 h/rt	8 h	**3d**/80	**5d**/20	**5d**/63	−
5	**1a**	methacrolein	**2a**	4 h/rt	8 h	**4a**/82	**6a**/75	**6a**/85	**7a**/45
6	**1b**		**2b**	4 h/rt	8 h	**4b**/85	**6b**/62	**6b**/87	**7b**/42
7	**1c**		**2c**	4 h/rt	8 h	**4c**/72	**6c**/77	**6c**/83	**7c**/49
8	**1d**		**2d**	4 h/reflux	8 h	**4d**/31	**6d**/60	**6d**/80	−
9	**1e**		**2e**	4 h/rt	8 h	**4e**/83	**6e**/79	**6e**/82	**7e**/44

(b) Generation of 1,5-Dienes. With the cycloadducts in hand, we turned our attention to finding suitable conditions to perform selective methylenation on the aldehyde. This was first carried out with Wittig reagent ($MePPh_3Br$/*n*-BuLi) at −78 °C and then raising the temperature to 0 °C to afford the desired vinylbicyclo-[2.2.2]octenones **5**−**6** in moderate yields (Scheme 2, Table 1). To our delight, methylenation with Lombardo reagent ($Zn/CH_2Br_2/TiCl_4$)[12] at 0 °C gave higher yields of the desired compounds. The structures of **5** and **6** were confirmed by NMR analyses. Their ^1H NMR spectra showed complete disappearance of aldehyde proton peak and three additional vinyl protons, while the ^{13}C NMR spectra revealed one carbonyl signal remained. Thus, the methylenation occurred on the aldehyde rather than the ketone. Many natural products with the decalin core and geminal dimethyl groups at the C5 position are known. Consequently, the aldehyde was transformed into an isopropylidene under *i*-$PrPPh_3I$/*n*-BuLi conditions and we envisaged to convert it into the corresponding *cis*-decalin core with geminal dimethyl groups at the C5 position.

(c) Cope Rearrangement of 1,5-Dienes. 1,5-Dienes **5**, **6**, and **7c** underwent Cope rearrangement smoothly at 180−250 °C in mesitylene with the addition of trimethyl orthoformate to remove traces of water present to furnish corresponding *cis*-decalins **8**, **9**, and **10c** in high yields (Scheme 2, Table 2). However, when diene **7a** was heated to 180 °C in mesitylene for 24 h, a mixture of **7a** and **10a** in a 2.3:1 ratio was obtained. The ratio of **7a** and **10a** was determined by the ^1H NMR analysis of their crude mixture. Unlike the anionic oxy-Cope rearrangement, the Cope rearrangement is a reversible reaction. During the course of the reaction, the equilibrium shifts toward the thermodynamically more stable product. To verify that the presence of **7a** in the reaction results from the reverse Cope rearrangement, compound **10a** was heated to 180 °C in mesitylene for 24 h again only to observe 2.3:1 mixture of **7a** and **10a**, confirming the usual trend of the Cope rearrangement. Compound **7b** showed a similar tendency, giving a 1:3.7 mixture of **7b** and **10b**. Surprisingly, compound **7e** did not give the desired product **10e**, presumably due to the steric clash between the geminal dimethyl and the 5,5-dimethyl-1,3-dioxanyl group at fused position in the *cis*-decalin (Table 2, entry 13). The thermal transformations of the cycloadducts examined are in

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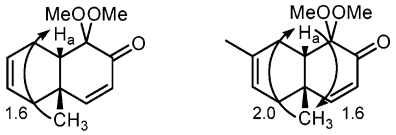
TABLE 2. Cope Rearrangement of 1,5-Dienes 5−7

		Cope rearrangement		
entry	1,5-diene	temp °C	time h	yield(%)
1	**5a**	200	8	**8a**/88
2	**5b**	200	8	**8b**/85
3	**5c**	200	8	**8c**/80
4	**5d**	200	8	**8d**/90
5	**6a**	250	8	**9a**/93
6	**6b**	180	24	**9b**/85
7	**6c**	250	8	**9c**/94
8	**6d**	180	24	**9d**/95
9	**6e**	180	24	**9e**/94
10	**7a**	180	24	**7a**/62 + **10a**/24
11	**7b**	180	24	**7b**/13 + **10b**/48
12	**7c**	180	24	**10c**/72
13	**7e**	250	12	—[a,b]

[a] A complex mixture was formed. [b] When the reaction was carried out at 180 or 200 °C, only recoverd starting material was observed.



8a **9a**

FIGURE 1. ^{1}H NMR studies of NOE (%) for **8a** and **9a**.

conformity with the general tendency of 1,5-dienes toward Cope rearrangement in which the position of equilibrium is influenced by the substitution pattern,[14] ring strain,[15] and conjugation.[16]

The stereochemistries of the *cis*-decalins **8a** and **9a** were determined with ^{1}H NMR nuclear Overhauser enhancement (NOE) experiments (Figure 1). In the case of **8a**, saturation of the bridge methyl protons gave rise to an increase in the signal intensity of H_a (1.6%) that suggested H_a and the bridge methyl group are of *cis*-relationship. Similarly, about 2% NOE was observed in the signal corresponding to H_a upon irradiation of the bridged methyl protons of **9a** indicating a *cis*-relationship between them. In the cases of the remaining decalins, the stereochemical assignments were based on analogy of the coupling patterns.

(d) Generation of Highly Substituted and Oxygenated *cis*-Decalins. Having developed an efficient stereocontrolled synthesis of *cis*-decalins, we envisaged extending these procedures to other bicyclo[2.2.2]octenones. Thus, we chose diones **11**[10] as alternative 1,5-diene precursors. The acetyl group in **11** was selectively methylenated by using the Lombardo reagent to give the isopropenyl compounds **12** (Scheme 3, Table 3), and these compounds had been converted to *cis*-decalins **13** in our previous studies.[8c] Alternatively, diones **11** were transformed into 5-silyloxy-1,5-diene species. In contrast to methylenation, 1,5-dienes were generated by enolization of the ketones followed by trapping with TMSOTf[13] to produce 5-silyloxy-1,5-dienes **14** in good yields.

Similarly, 5-silyloxy-1,5-dienes **14** underwent Cope rearrangement smoothly at 200 °C to generate the desired *cis*-decalins **15** in excellent yields (Scheme 3, Table 3). It is noteworthy that compound **14a** under the similar reaction conditions provided **15a** by Cope rearrangement and sequential double bond migration. The ^{1}H NMR of **15a** showed the vinyl proton as a singlet at δ 4.65 which suggested the double bond had migrated, while in compounds **16b−d** the vinyl proton appeared as a doublet of doublet of doublets at δ 4.64−4.72. A semiempirical calculation at the PM3 level estimated the double bond migration product **15a** has lower heat of formation than the unmigrated product **16a**. For the other three *cis*-decalins **15b−d**, the calculation showed the reverse results. Silyl enol ether in **15** and **16** was further hydrolyzed under 1% aqueous oxalic acid[17] to give diones **17** in high yields.

(e) Total Syntheses of Eremopetasidione, 3β-Angeloyloxyfuranoeremophilane, and 3β-Methacryloyloxyfuranoeremophilane. After the efficient four-step stereocontrolled synthesis of *cis*-decalins, we decided to apply this strategy to the total syntheses of eremopetasidione, 3β-angeloyloxyfuranoeremophilane, and 3β-methacryloyloxyfuranoeremophilane.

The eremophilane family is a large, structurally diverse group of sesquiterpenoids characterized by a decalin skeleton in which a methyl migration has taken place to produce a non-isoprenoid substituent pattern.[18] A subset of this group, the furanoeremophilanes, bear a furan ring fused onto the bicyclic eremophilane system.[18b] The diverse biological properties of eremophilane, combined with the unique structural and conformational challenges, have attracted considerable synthetic attention.[19]

(−)-Eremopetasidione is a norsesquiterpenoid that was isolated[20] from rhizomes of *Petasites japonicus* MAXIM and has interesting medicinal properties.[21] 3β-Angeloyloxyfuranoeremophilane and 3β-methacryloyloxyfuranoeremophilane were isolated from *Frafugium japonicum* Kitamura[22] and *Othonna macrophylla* DC,[23] respectively.

Our retrosynthetic analysis is summarized in Scheme 4. Eremophilanes **18**, **19**, and **20** could be synthesized from the same intermediate **21** via the C-acetylation and dehydrogenation for **18** and via aldol reaction, dehydration, and esterification for **19** and **20**. The common intermediate **21** could be obtained from *cis*-decalin **22** via hydrolysis and reduction. The intermediate **22** would be generated by the use of our methodology described above by the Cope rearrangement of 2-silyloxy-1,5-dienone **23** followed by double bond migration,[7] and **23** could be obtained from bicyclo[2.2.2]octenone derivative **24**. Access to this cycloadduct was to be gained from creosol (**1a**) and ethyl vinyl ketone via Diels−Alder cycloaddition of in situ generated MOB **2a**.

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SCHEME 3

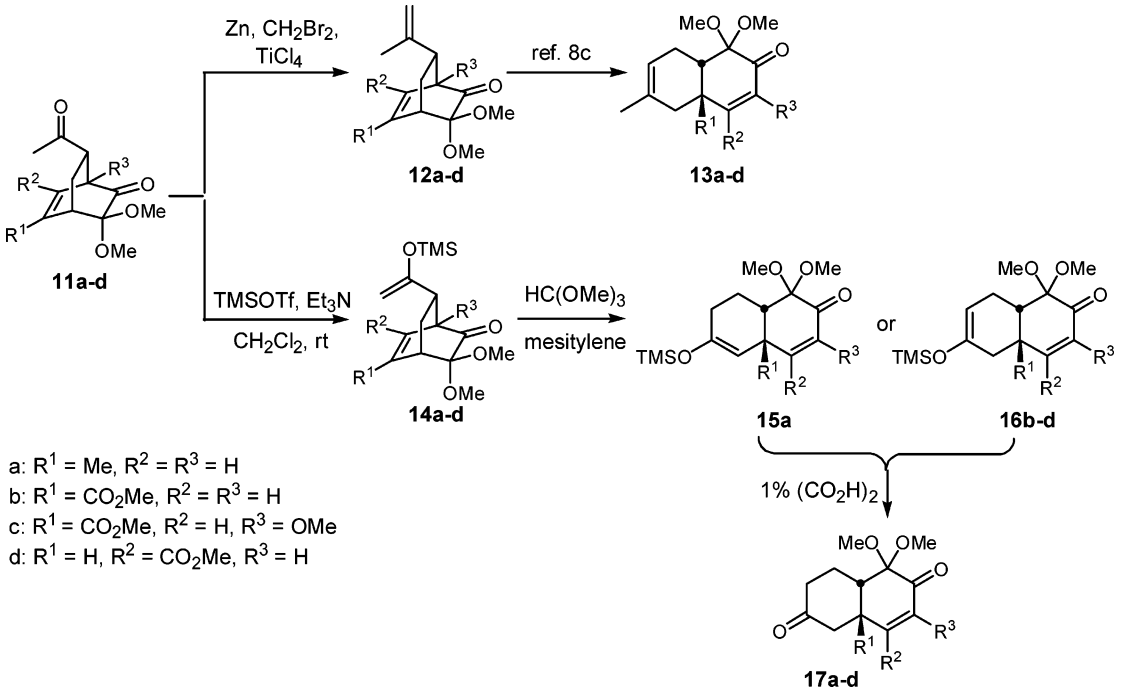
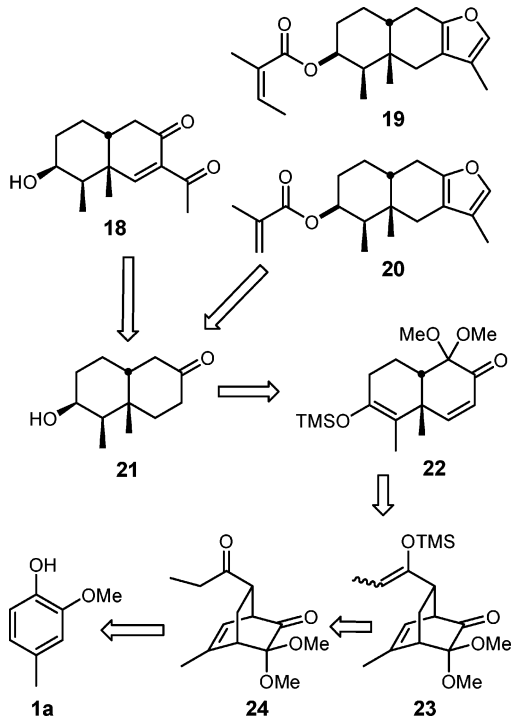


TABLE 3. Preparation of Highly Substituted and Oxygenated *cis*-Decalins

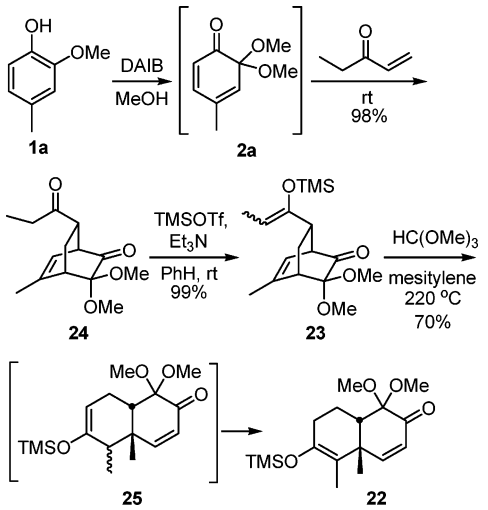
		olefination		Cope rearrangement of **14**			
entry	cycloadduct	Zn, CH_2Br_2, $TiCl_4$/yield(%)	silyl enol ether/yield(%)	temp °C	time h	yield(%)	hydrolyzis/yield(%)
1	**11a**	**12a**/75	**14a**/80	200	8	**15a**/93	**17a**/98
2	**11b**	**12b**/67	**14b**/86	200	8	**16b**/95	**17b**/95
3	**11c**	**12c**/61	**14c**/89	200	8	**16c**/97	**17c**/97
4	**11d**	**12d**/60	**14d**/89	200	8	**16d**/89	**17d**/96

The bicyclo[2.2.2]octenone **24** was prepared as a single isomer in excellent yield from the regio- and stereocontrolled intermolecular Diels−Alder reaction of ethyl vinyl ketone and MOB **2a**, which was generated in situ by the oxidation of creosol with diacetoxyiodobenzene (DAIB) in MeOH (Scheme 5). The *n*-propanoyl side chain of **24** was then converted into silyl enol ether **23** as an inseparable 1:1 mixture of *cis*- and *trans*- isomers at the newly formed double bond. This was followed by Cope rearrangement at 220 °C to give the *cis*-decalin product **22** as the single isolable product in 70% yield. The structure of **22** was determined by ^{1}H NMR and ^{13}C NMR spectra. Its ^{1}H NMR

SCHEME 4



SCHEME 5



SCHEME 6

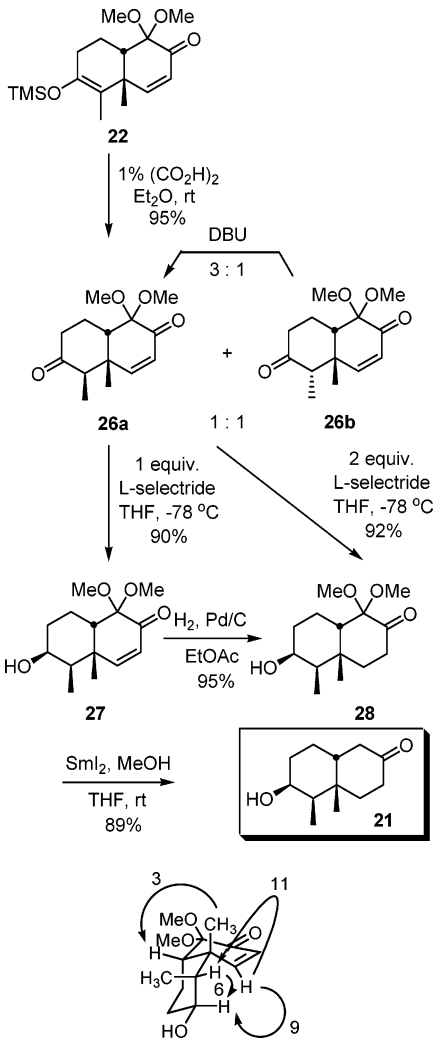


FIGURE 2. ^{1}H NMR studies of NOE (%) for **27**.

spectrum showed only two vinyl proton signals (δ 5.81, 6.76) and an allylic methyl (δ 1.65) signal. After the Cope rearrangement, the trisubstituted double bond in **25** was isomerized into the thermodynamically more stable tetrasubstituted double bond to yield **22**.

After effectively constructing the *cis*-decalin core **22** from **1a** in good yield, we proceeded to install the remaining two stereogenic centers. Exposure of **22** to 1% aqueous oxalic acid gave a mixture of separable epimers **26a**, **26b** in a 1:1 ratio (Scheme 6). The ratio of **26a** and **26b** was determined by the ^{1}H NMR analysis of their crude mixture. Exposure of **26b** to acidic conditions (e.g., $H_2C_2O_4$, *p*TSA) resulted in the formation of **26a** and **26b** in 1:1 ratio, whereas the use of DBU led to a 3:1 ratio. The selective reduction of **26a** took place with 1 equiv of L-selectride at −78 °C to furnish alcohol **27** as a single diastereomer in 90% yield, which bears the required four contiguous stereogenic centers. The stereochemistry of intermediate **27** was established by ^{1}H NMR NOE (Figure 2) and further confirmed by X-ray diffraction studies.[24] The conjugated ketone **27** was hydrogenated with 10% Pd/C to produce ketone **28**. Alternatively, **28** could be obtained from **26a** directly in 92% yield when reduced with 2 equiv of L-selectride.

(24) See Supporting Information.

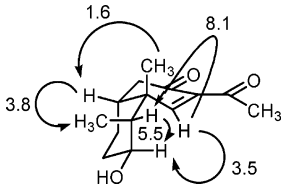
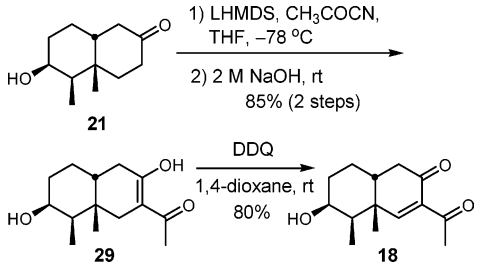


FIGURE 3. ^{1}H NMR studies of NOE (%) for **18**.

SCHEME 7



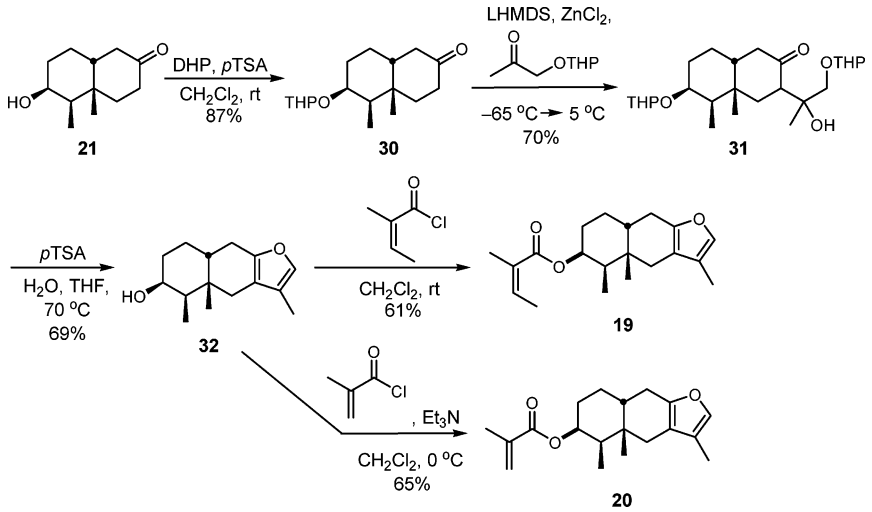
Demethoxylation[25] of **28** with samarium diiodide in THF in the presence of MeOH as a proton source gave the advanced intermediate **21**.

The next step in the synthesis required the introduction of an acetyl group by selective C-acetylation of the enolate derived from **21**. In order to give a highly regioselective C- vs O-acetylation, we used pyruvonitrile (acetyl cyanide)[26] as an acetylation agent rather than acetyl halide. Thus, regioselective deprotonation of **21** with LHMDS at −78 °C followed by reaction with pyruvonitrile, and subsequent treatment with 2 M NaOH, produced **29** in 85% yield (Scheme 7). The reason for formation of the desired enolate is due to the fact that deprotonation occurred at the less hindered carbon when a bulky base was used. Finally, dehydrogenation of enol **29** was effected with DDQ[27] to accomplish the total synthesis of (±)-eremopetasidione (**18**).[9c] The structure of **18** was elucidated by ^{1}H−^{1}H and ^{1}H−^{13}C COSY and NOE (Figure 3) studies. The ^{1}H and ^{13}C NMR spectral data of synthetic **18** are identical with those of natural (−)-**18**.

Attention was now turned to the establishment of the furan ring (Scheme 8). To this end the hydroxyl group in **21** was protected as a THP group. Regioselective deprotonation with LHMDS at −65 °C gave the lithium enolate, which was then converted to the zinc enolate[28] and subsequently treated with acetonyl tetrahydropyranyl ether.[29] The temperature was gradually raised to 5 °C over 1.5 h to furnish the aldol product **31** in 70% yield. Compound **31** on treatment with *p*TSA in THF and water at 70 °C gave a furan-fused *cis*-decalin **32** by the removal of protecting groups.[22] Finally, furan **32** was independently reacted with angeloyl chloride[30] and methacryloyl chloride to finish the total syntheses of (±)-3β-angeloyloxyfuranoeremo-

(25) Hwang, J.-T.; Liao, C.-C. *Tetrahedron Lett.* **1991**, *32*, 6583.
(26) Oliveira-Ferrer, L.; Schmidt, K.; Margaretha, P. *Helv. Chim. Acta* **2001**, *84*, 3818.
(27) Edwards, J. A.; Calzada, M. C.; Ibánez, L. C.; Rivera, M. E. C.; Urquiza, R.; Cardona, L.; Orr, J. C.; Bowers, A. *J. Org. Chem.* **1964**, *29*, 3481.
(28) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.
(29) Hagiwara, H.; Uda, H.; Kodama, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 963.
(30) (a) Beeby, P. *Tetrahedron Lett.* **1977**, 3379. (b) Torres-Valencia, J. M.; Cerda-García-Rojas, C. M.; Joseph-Nathan, P. *Tetrahedron: Asymmertry* **1998**, *9*, 757.

SCHEME 8



philane (**19**) and (±)-3β-methacryloyloxyfuranoeremophilane (**20**), respectively. The ^{1}H NMR and IR spectra of **19** and **20** were in good agreement with those reported in the literature.[22,23]

Conclusion

In summary, an efficient and general stereocontrolled strategy to synthesize polyfunctionalized *cis*-decalins from 2-methoxyphenols was developed. This new approach had entirely overcome the shortcomings of the earlier method to construct polyfunctionalized *cis*-decalins via the intermolecular Diels−Alder reaction of MOBs with unactivated acyclic dienes. This methodology was successfully applied to the total syntheses of (±)-eremopetasidione (**18**), (±)-3β-angeloyloxyfuranoeremophilane (**19**), and (±)-3β-methacryloyloxyfuranoeremophilane (**20**) via the common intermediate **21**, which was derived from creosol.

Experimental Section

The analytical data for compounds **5b**−**c**, **6a**−**d**, **8b**−**c**, **9a**−**d**, and **12** are identical with those already reported in the literature.[8c]

General Procedure for the Diels−Alder Reactions of MOBs. To a mixture of a 2-methoxyphenol (5 mmol) and a dienophile (125 mmol) in anhydrous methanol (30 mL) was added a solution of DAIB (6 mmol) in MeOH (30 mL) over 4 h using a syringe pump at room temperature under nitrogen atmosphere. The stirring was continued for a further 8 h, and then MeOH and excess dienophile were removed. The residue was purified by silica-gel column chromatography with EtOAc/hexanes as eluent to furnish the pure adducts **3**−**4**.

(1*R,4*R**,7R*)-7-Formyl-3,3-dimethoxy-5-methylbicyclo[2.2.2]-oct-5-en-2-one (3a).** Colorless oil; IR (neat) ν 3045, 2947, 2835, 1736, 1646, 1443, 1319, 1135, 1071, 784 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (ddd, J = 2.8, 6.0, 13.2 Hz, 1H), 1.86 (d, J = 1.6 Hz, 3H), 2.06 (ddd, J = 3.2, 10.0, 13.2 Hz, 1H), 2.93 (apparent dd, J = 2.0, 6.0, 10.0 Hz, 1H), 2.95 (ddd, J = 1.6, 2.8, 3.2 Hz, 1H), 3.29 (s, 3H), 3.32 (s, 3H), 3.42 (dd, J = 2.0, 6.4 Hz, 1H), 5.61 (ddd, J = 1.6, 1.6, 6.4 Hz, 1H) 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 21.1, 43.5, 47.2, 47.5, 50.6, 94.6, 116.8, 146.8, 199.9, 200.8; MS (EI, 70 eV) *m*/*z* (% base peak) 196 (M^+ − 28, 94), 181 (8), 167 (86), 153 (18), 133 (27), 105 (15), 93 (52), 91 (45), 77 (40), 43 (100); HRMS (EI) calcd for $C_{11}H_{16}O_3$ (M^+ − 28) 196.1099, Found 196.1096.

General Procedures for Methylenation. (i) Wittig Reagent. To a stirred solution of $MePPh_3Br$ (1 mmol) in THF (10 mL) was added *n*-BuLi (0.75 mmol) at 0 °C. After stirred at 0 °C for 1 h then cooled to −78 °C, a solution of bicyclo[2.2.2]octenone (0.5 mmol) in THF (5 mL) was added and warmed to 0 °C. The reaction was monitored by TLC, and after completion of the reaction, the mixture was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography with EtOAc/hexanes as eluent to furnish the pure products **5**−**6**.

(ii) Lombardo Reagent. To a stirred solution of bicyclo[2.2.2]-octenone (0.5 mmol) in CH_2Cl_2 (10 mL) was added excess Lombardo reagent at 0 °C. After stirred at this temperature for 0.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and filtered through a pad of Celite. The aqueous phase was extracted with Et_2O and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography with EtOAc/hexanes as eluent to furnish the pure products **5**−**6**, **12**.

(1*R,4*R**,7*S**)-3,3-Dimethoxy-5-methyl-7-vinylbicyclo[2.2.2]-oct-5-en-2-one (5a).** Colorless oil; IR (neat) ν 2949, 2835, 1737, 1639, 1605, 1445, 1148, 1081, 914, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.17 (ddd, J = 3.0, 5.2, 13.2 Hz, 1H), 1.89 (d, J = 1.2 Hz, 3H), 2.18 (ddd, J = 2.8, 9.6, 13.2 Hz, 1H), 2.75 (m, 1H), 2.85 (dd, J = 3.0, 5.2 Hz, 1H), 2.95 (dd, J = 1.8, 6.4 Hz, 1H), 3.29 (s, 3H), 3.32 (s, 3H), 4.91 (d, J = 9.8 Hz, 1H), 4.97 (d, J = 16.8 Hz, 1H), 5.56 (ddd, J = 8.0, 9.8, 16.8 Hz, 1H), 5.65 (apparent d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ21.0, 27.2, 38.6, 43.8, 49.6, 50.3, 53.2, 94.1, 114.0, 117.3, 140.7, 145.2, 197.9, 202.2; MS (EI, 70 eV) *m*/*z* (% base peak) 194 (M^+ − 28, 90), 179 (22), 163 (11), 147 (15), 131 (13), 119 (100), 105 (51), 91 (71), 75 (54), 59 (35); HRMS (EI) calcd for $C_{13}H_{18}O_3$ 222.1256, Found 222.1250.

General Procedure for Isopropylidenation. To a mixture of *i*-$PrPPh_3I$ (0.5 mmol) and HMPA (1.25 mL) in THF (2.5 mL) was added *n*-BuLi (0.375 mmol) at −60 °C. After stirred at −60 °C for 10 min, a solution of bicyclo[2.2.2]octenone (0.25 mmol) in THF (1.25 mL) was added and warmed to −10 °C. When TLC showed no more starting material, the mixture was diluted with Et_2O and filtered. The organic layer was washed successively with saturated aqueous NH_4Cl, water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography with EtOAc/hexanes as eluent to furnish the pure products **7**.

(1*R,4*R**,7*S**)-3,3-Dimethoxy-5,7-dimethyl-7-(2-methyl-1-propenyl)bicyclo[2.2.2]oct-5-en-2-one (7a).** Colorless oil; IR (neat) ν 2963, 2944, 2871, 1736, 1441, 1376, 1132, 1085, 1054, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.60 (d, J = 0.8 Hz,

3H), 1.64 (d, J = 0.8 Hz, 3H), 1.78 (dd, J = 3.6, 12.8 Hz, 1H), 1.87 (d, J = 2.0 Hz, 3H), 2.07 (dd, J = 2.4, 12.8 Hz, 1H), 2.78−2.82 (m, 2H), 3.31 (s, 3H), 3.32 (s, 3H), 5.12 (apparent s, 1H), 5.73 (ddq, J = 1.6, 2.0, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.2, 26.7, 27.7, 38.4, 39.8, 44.8, 49.5, 50.3, 61.3, 94.1, 119.9, 131.9, 135.5, 145.2, 203.9; MS (EI, 70 eV) *m*/*z* (% base peak) 264 (M^+, 7), 236 (100), 221 (14), 205 (15), 189 (13), 161 (22), 153 (31), 124 (19), 96 (41), 74 (17); HRMS (EI) calcd for $C_{16}H_{24}O_3$ 264.1725, Found 264.1723.

General Procedure for Cope Rearrangement. To a solution of **5**−**7**, **14** (100 mg) in mesitylene (5 mL) was added trimethyl orthoformate (0.5 mL), and the resulting mixture was degassed with argon for 30 min. The reaction mixture was then heated for a period of time (see Table **2**−**3** for the duration of heating and temperature), cooled to room temperature, and concentrated using a Kugelrohr apparatus. The residue was obtained was purified by silica-gel column chromatography using EtOAc/hexanes as eluent to furnish the pure *cis*-decalin products.

(4a*R,8a*R**)-1,1-Dimethoxy-2-oxo-4a-methyl-1,2,4a,5,8,8a-hexahydro-2-naphthalenone (8a).** Colorless oil; IR (neat) ν 3024, 2931, 1688, 1620, 1449, 1390, 1252, 1154, 1074, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.80−2.20 (m, 4H), 2.35 (ddd, J = 1.4, 7.8, 9.4 Hz, 1H), 3.18 (s, 3H), 3.26 (s, 3H), 5.63 (m, 2H), 5.86 (d, J = 10.0 Hz, 1H), 6.60 (d, J = 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 30.1, 37.0, 38.8, 42.1, 48.3, 50.4, 99.7, 124.3, 125.7, 159.2, 192.3; MS (EI, 70 eV) *m*/*z* (% base peak) 222 (M^+, 72), 191 (41), 179 (12), 162 (28), 149 (46), 134 (100), 119 (50), 91 (50), 77 (20), 55 (13); HRMS (EI) calcd for $C_{13}H_{18}O_3$ 222.1255, Found 222.1248.

General Procedure for Silyl Enol Ether Formation. To a stirred solution of **11** (1 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (1.4 mmol) and TMSOTf (1.5 mmol) at 0 °C. After stirred at 0 °C for 3 h then warmed to room temperature and stirred for another 3 h. $NaHCO_3$ (3 mmol) was added then filtered and concentrated. The crude product was purified by flash silica-gel chromatography with EtOAc/hexanes as eluent to furnish the pure products **14**.

(1*R,4*R**,7*R**)-3,3-Dimethoxy-7-(1-trimethylsilyloxyvinyl)-5-methylbicylco[2.2.2]oct-5-en-2-one (14a).** Colorless oil; IR (neat) ν 2950, 1740, 1632, 1446, 1253, 1212, 1128, 1084, 848, 787 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.30 (ddd, J = 3.6, 9.6, 13.2 Hz, 1H), 1.87 (d, J = 1.5 Hz, 3H), 2.11 (ddd, J = 2.8, 6.4, 13.2 Hz, 1H), 2.68 (m, 1H), 2.85 (apparent dd, J = 2.8, 3.6 Hz, 1H), 3.13 (dd, J = 1.5, 5.8 Hz, 1H), 3.30 (s, 3H), 3.33 (s, 3H), 4.00 (s, 2H), 5.62 (apparent d, J = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.1, 20.8, 25.7, 39.8, 43.7, 49.7, 50.2, 51.6, 89.4, 94.0, 117.9, 143.6, 159.4, 201.2; MS (EI, 70 eV) *m*/*z* (% base peak) 310 (M^+, 2), 282 (65), 267 (84), 235 (21), 207 (30), 192 (82), 171 (85), 165 (100), 107 (60), 73 (87); HRMS (EI) calcd for $C_{16}H_{26}O_4Si$ 310.1600, Found 310.1576.

General Procedure for Hydrolysis. To a stirred solution of **15** or **16** (100 mg) in Et_2O (2 mL) was added 1% aqueous oxalic acid (2 mL). After stirred at room temperature for 18 h, the organic layer was separated. The aqueous phase was extracted with Et_2O and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography with EtOAc/hexanes as eluent to furnish the pure diones **17**.

(4a*R,8a*S**)-5,5-dimethoxy-8a-methyl-1,2,3,4,4a,5,6,8a-octahydro-2,6-naphthalenedione (17a).** Colorless oil; IR (neat) ν2949, 2836, 1746, 1736, 1686, 1457, 1422, 1218, 1088, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.80−2.00 (m, 2H), 2.20−2.50 (m, 3H), 2.27 (d, J = 14.4 Hz, 1H), 2.51 (d, J = 14.4 Hz, 1H), 3.13 (s, 3H), 5.84 (d, J = 10.4 Hz, 1H), 6.43 (dd, J = 1.6, 14.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 29.6, 38.6, 42.2, 44.0, 50.7, 52.3, 99.4, 124.8, 155.2, 192.4, 209.9; MS (EI, 70 eV) *m*/*z* (% base peak) 238 (M^+, 1), 210 (24), 207 (19), 192 (7), 167 (7), 141 (13), 128 (24), 101 (100), 91 (23), 77 (23); HRMS (EI) calcd for $C_{13}H_{18}O_4$ 238.1204, Found 238.1196.

(1*S,4*S**,7*S**)-3,3-Dimethoxy-5-methyl-7-propionyl-bicyclo-[2.2.2]oct-5-en-2-one (24).** To a mixture of 2-methoxy-4-mehtylphenol (**1a**) (1.0 g, 7.24 mmol) and ethyl vinyl ketone (4.9 g, 57.9 mmol) in methanol (50 mL) was added a solution of PhI-$(OAc)_2$ (2.8 g, 8.69 mmol) in MeOH (25 mL), and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4:1) to afford **24** (1.80 g, 98%) as a colorless solid. Analytically pure **24** was obtained by crystallization from Et_2O−hexane: mp 55.7−56 °C; IR (neat) ν 2944, 2836, 1738, 1714, 1445, 1135, 1092, 1052, 963, 825 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (dd, J = 7.6, 7.6 Hz, 3H), 1.72 (ddd, J = 3.2, 6.4, 12.4 Hz, 1H), 1.89 (d, J = 1.6 Hz, 1H), 2.11 (ddd, J = 2.8, 9.6, 12.4 Hz, 1H), 2.44 (dq, J = 7.6, 10.4 Hz, 1H), 2.48 (dq, J = 7.6, 10.4 Hz, 1H), 2.94−2.96 (m, 1H), 3.04 (ddd, J = 1.6, 6.4, 9.6 Hz, 1H), 3.33 (s, 3H), 3.35 (s, 3H), 3.34−3.35 (m, 1H), 5.63−5.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 20.9, 22.9, 34.1, 43.7, 46.0, 49.4, 49.7, 50.4, 94.2, 117.1, 145.3, 201.2, 208.8; MS (EI, 70 eV) *m*/*z* (% base peak) 224 (M^+ − 28, 100), 193 (6), 177 (6), 167 (93), 135 (9), 91 (9), 75 (22), 57 (21), 28 (25), 18 (68); HRMS (EI) calcd for $C_{13}H_{20}O_3$ (M^+ − 28) 224.1412, Found 224.1412; Anal.Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.75; H, 8.00.

(1*S,*S**,7*R**)-3,3-Dimethoxy-5-methyl-7-{1-[(1,1,1-trimethylsilyl)-oxy]-1-propenyl}bicyclo[2.2.2]-oct-5-en-2-one (23).** To a stirred solution of **24** (1.66 g, 6.58 mmol) in benzene (30 mL) was added Et_3N (2.0 g, 19.7 mmol) and TMSOTf (2.4 mL, 13.2 mmol). After stirred at room temperature for 2 h, $NaHCO_3$ (3.32 g, 39.5 mmol) was added to the solution, and stirred for another 30 min. The mixture was filtered and concentrated. The crude product was purified by flash silica-gel chromatography (hexane/EtOAc = 10:1) to afford **23** (2.11 g, 99%) as a yellowish oil. IR (neat) ν 3048, 2958, 2835, 1739, 1662, 1445, 1253, 1087, 1048, 923, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 0.19 (s, 9H), 1.29 (ddd, J = 2.8, 7.2, 13.2 Hz, 1H), 1.38 (ddd, J = 2.4, 6.8, 12.4 Hz, 1H), 1.50 (dd, J = 1.4, 6.8 Hz, 3H), 1.54 (d, J = 7.2 Hz, 3H), 1.88 (d, J = 1.2 Hz, 3H), 1.89 (d, J = 1.6 Hz, 3H), 2.03−2.13 (m, 2H), 2.64 (dd, J = 8.0, 8.0 Hz, 1H), 2.86−2.89 (m, 2H), 2.96 (dd, J = 1.6, 6.4 Hz, 1H), 3.12 (dd, J = 8.0, 8.0 Hz, 1H), 3.21 (dd, J = 1.6, 6.8 Hz, 1H), 3.32 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.36 (s, 3H), 4.49 (q, J = 6.8 Hz, 1H), 4.52 (q, J = 7.2 Hz, 1H), 5.63−5.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.2, 0.5, 10.9, 11.4, 20.7, 20.9, 25.2, 25.5, 33.6, 39.7, 43.5, 43.8, 49.6, 49.7, 50.2, 50.3, 51.1, 52.2, 94.0, 94.1, 99.8, 101.8, 117.7, 118.4, 142.0, 144.0, 151.2, 152.1, 201.6, 202.1; MS (EI, 70 eV) *m*/*z* (% base peak) 324 (M^+, 6), 296 (93), 281 (85), 249 (18), 206 (26), 191 (36), 165 (43), 131 (31), 72 (81), 28, (36) 18 (100); HRMS (EI) calcd for $C_{17}H_{28}O_4Si$ 324.1757, Found 324.1757.

(4a*S,6a*S**)-1,1-Dimethoxy-4a,5-dimethyl-6-trimethylsilyloxy-1,2,4a,7,8,8a-hexahydro-2-naphthalenone (22).** A mixture of **23** (100 mg, 0.308 mmol), 1,3,5-trimethylbenzene (5 mL) and trimethyl orthoformate (0.5 mL) in a seal tube was heated to 220 °C for 48 h. After removed the solvent in vacuo, the crude product was purified by silica-gel column chromatography (hexane/EtOAc = 10:1) to give **22** (70 mg, 70%) as a yellowish oil. IR (neat) ν 2959, 2934, 2836, 1698, 1671, 1453, 1355, 1252, 1115, 1059, 919, 860, 844, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.23−1.34 (m, 1H), 1.49 (s, 3H), 1.64−1.65 (m, 3H), 1.68−1.74 (m, 1H), 1.95−2.05 (m, 1H), 2.10−2.21 (m, 2H), 3.16 (s, 3H), 3.29 (s, 3H), 5.81 (d, J = 10.8 Hz, 1H), 6.76 (dd, J = 1.6, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.6, 10.6, 21.0, 26.7, 30.1, 42.7, 46.0, 47.2, 50.2, 99.8, 116.3, 122.5, 146.3, 153.4, 193.0; MS (EI, 70 eV) *m*/*z* (% base peak) 324 (M^+, 3), 309 (6), 292 (17), 264 (27), 252 (56), 224 (43), 193 (8), 167 (42), 101 (50), 18 (100); HRMS (EI) calcd for $C_{17}H_{28}O_4Si$ 324.1757, Found 324.1752.

(1*R,4a*S**,8a*S**)-5,5-Dimethoxy-1,8a-dimethyl-1,2,3,4,4a,5,6,-8a-octahydro-2,6-naphthalenedione (26a) and (1*R**,4a*S**,8a*R**)-5,5-dimethoxy-1,8a-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-2,6-naphthalenedione (26b).** To a stirred solution of **22** (1.0 g, 3.08 mmol) in Et_2O (15 mL) was added 1% aqueous oxalic acid (15 mL). After stirred at room temperature for 18 h, the organic layer was separated. The aqueous phase was extracted with Et_2O and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 2:1) to afford **26a** (373 mg, 48%) as a colorless solid and **26b** (365 mg, 47%) as a yellow oil. Analytically pure **26a** was obtained by crystallization from Et_2O−hexane: mp 91.5−92.5 °C; IR (neat) ν 2973, 2942, 2836, 1708, 1691, 1623, 1459, 1378, 1121, 1083, 1069, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.8 Hz, 3H), 1.18 (s, 3H), 1.88−1.96 (m, 1H), 2.04−2.13 (m, 1H), 2.20 (dd, J = 4.5, 8.0 Hz, 1H), 2.29 (ddd, J = 6.6, 6.6, 16.0 Hz, 1H), 2.65 (ddd, J = 7.0, 7.0, 16.0 Hz, 1H), 2.97 (q, J = 6.8 Hz, 1H), 3.21 (s, 3H), 3.29 (s, 3H), 5.98 (d, J = 10.2 Hz, 1H), 6.69 (d, J = 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 20.2, 22.7, 38.5, 43.8, 44.7, 48.8, 49.9, 51.0, 99.7, 124.6, 155.1, 192.4, 213.3; MS (EI, 70 eV) *m*/*z* (% base peak) 252 (M^+, 29), 221 (10), 167 (5), 116 (7), 101 (100), 88 (11), 55 (7), 28 (22), 18 (56); HRMS (EI) calcd for $C_{14}H_{20}O_4$ 252.1362, Found 252.1363. Anal.Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.78; H, 8.08. **26b**: IR (neat) ν 2972, 2943, 2836, 1714, 1697, 1619, 1453, 1379, 1140, 1097, 1053, 1004, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, J = 6.4 Hz, 3H), 1.57 (s, 3H), 1.71−1.81 (m, 1H), 2.02−2.11 (m, 1H), 2.17−2.25 (m, 1H), 2.33−2.41 (m, 1H), 2.62−2.68 (m, 1H), 3.17 (s, 3H), 3.33 (s, 3H), 5.92 (d, J = 10.4 Hz, 1H), 6.62 (dd, J = 1.6, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 22.6, 28.1, 38.1, 45.5, 45.9, 47.5, 50.2, 53.4, 99.4, 126.2, 150.8, 192.4, 210.7; MS (EI, 70 eV) *m*/*z* (% base peak) 252 (M^+, 24), 221 (10), 129 (7), 116 (7), 109 (16), 101 (100), 88 (11), 55 (7), 28 (22), 18 (66); HRMS (EI) calcd for $C_{14}H_{20}O_4$ 252.1362, Found 252.1363.

(4a*R,5*R**,6*S**,8a*S**)-6-Hydroxy-1,1-dimethoxy-4a,5-dimethyl-1,2,4a,5,6,7,8,8a-octahydro-2-naphthalenone (27).** To a stirred solution of **26a** (311 mg, 1.23 mmol) in THF (15 mL) at −78 °C was added L-selectride (1 M in THF, 1.6 mL, 1.6 mmol). The reaction mixture was stirred at −78 °C for 30 min and then stirred at room temperature for another 30 min. The mixture was quenched with 2 M NaOH (3.2 mL) and 35% H_2O_2 (1.6 mL), and stirred at room temperature for 10 min. The solution was extracted with EtOAc and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 2:1) to give **27** (280 mg, 90%) as a colorless solid. Analytically pure **27** was obtained by crystallization from EtOAc−hexane: mp 107.5−108 °C; IR (neat) ν 3451, 2939, 1686, 1461, 1382, 1142, 1093, 1042, 945, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 7.4 Hz, 3H), 1.33 (s, 3H), 1.60−1.75 (m, 5H), 1.78 (dq, J = 4.4, 7.4 Hz, 1H), 2.25 (ddd, J = 2.2, 5.2, 12.4 Hz, 1H), 3.12 (s, 3H), 3.24 (s, 3H), 3.64 (ddd, J = 4.4, 4.4, 11.2 Hz, 1H), 5.86 (d, J = 10.0 Hz, 1H), 6.58 (dd, J = 2.2, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.7, 22.4, 27.2, 28.6, 40.1, 42.6, 47.0, 47.2, 50.0, 70.1, 99.7, 125.0, 158.9, 193.1; MS (EI, 70 eV) *m*/*z* (% base peak) 254 (M^+, 6), 236 (8), 223 (10), 208 (11), 179 (2), 145 (30), 123 (18), 101 (100), 79 (19), 43 (18); HRMS (EI) calcd for $C_{14}H_{22}O_4$ 254.1519, Found 254.1525. Anal.Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.72; H, 8.76.

(4a*R,5*R**,6*S**,8a*S**)-6-Hydroxy-1,1-dimethoxy-4a,5-dimethylperhydro-2-naphthalenone (28).** A mixture of **27** (100 mg, 0.39 mmol) and 10% Pd/C (10 mg) in EtOAc (5 mL) was stirred under a hydrogen balloon at room temperature for 36 h. Filtration and concentration in vacuo gave a residue, which was purified by silica-gel column chromatography (hexane/EtOAc = 4:1) to give **28** (95 mg, 95%) as a colorless solid. Analytically pure **28** was obtained by crystallization from Et_2O−hexane: mp 108−108.5 °C; IR (neat) ν 3470, 2939, 2871, 2835, 1732, 1462, 1137, 1089, 1061, 1004, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 7.2 Hz, 3H), 1.02 (m, 1H), 1.33 (s, 3H), 1.33−1.48 (m, 3H), 1.57−1.70 (m, 3H), 2.17 (ddd, J = 2.4, 4.4, 13.2 Hz, 1H), 2.24−2.35 (m, 2H), 2.83−2.92 (m, 1H), 3.13 (s, 3H), 3.23 (s, 3H), 4.01−4.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 22.1, 26.6, 28.0, 33.3, 35.8, 37.8, 42.5, 45.5, 47.3, 49.8, 68.0, 102.4, 207.5; MS (EI, 70 eV) *m*/*z* (% base peak) 256 (M^+, 1), 196 (37), 181 (25), 164 (11), 143 (11), 125 (15), 101 (100), 74 (8), 58 (21), 28 (32), 18 (61); HRMS (EI) calcd for $C_{14}H_{24}O_4$ 256.1675, Found 256.1683. Anal.Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.57; H, 9.42.

(4a*R,5*R**,6*S**,8a*S**)-6-Hydroxy-1,1-dimethoxy-4a,5-dimethylperhydro-2-naphthalenone (28).** To a stirred solution of **26a** (100 mg, 0.40 mmol) in THF (5 mL) at −78 °C was added L-selectride (1 M in THF, 1 mL, 1 mmol). The reaction mixture was stirred at −78 °C for 30 min and then stirred at room temperature for another 30 min. The mixture was quenched with 2 M NaOH (2 mL) and 35% H_2O_2 (1 mL), and stirred at room temperature for 10 min. The solution was extracted with EtOAc and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4:1) to give **28** (93 mg, 92%) as a colorless solid.

(4a*S,5*R**,6*S**,8a*R**)-6-Hydroxy-4a,5-dimethylperhydro-2-naphthalenone (21).** To a stirred solution of **28** (41 mg, 0.16 mmol) in methanol (0.2 mL) was added SmI_2 (0.1 M in THF, 11.2 mL, 1.12 mmol) at room temperature under N_2 atmosphere. After stirred for 40 min, the solvent was evaporated. The residue was dissolved in water and 2 M HCl, and extracted with EtOAc. The combined extracts were washed brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica-gel chromatography (hexane/EtOAc = 1:1) to give **21** (28 mg, 89%) as a white solid. Analytically pure **21** was obtained by crystallization from Et_2O−hexane: mp 92−93 °C (Et_2O−hexane); IR (neat) ν 3444, 2936, 2871, 1712, 1463, 1338, 1203, 1073, 1029, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 7.6 Hz, 3H), 1.16−1.27 (m, 1H), 1.22 (s, 3H), 1.37−1.44 (m, 1H), 1.50−1.60 (m, 1H), 1.68−1.82 (m, 4H), 1.91−1.97 (m, 1H), 2.18−2.30 (m, 3H), 2.40−2.62 (m, 2H), 4.05 (ddd, J = 4.4, 4.4, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 23.9, 26.3, 28.7, 33.6, 35.8, 37.6, 39.3, 41.2, 43.0, 69.2, 212.3; MS (EI, 70 eV) *m*/*z* (% base peak) 196 (M^+, 16), 178 (89), 163 (100), 136 (21), 124 (41), 107 (26), 95 (29), 80 (22), 55 (29), 41 (29), 18 (23); HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1463, Found 196.1463. Anal.Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.44; H, 10.34.

1-[(4a*R,7*S**,8*R**,8a*S**)-3,7-Dihydroxy-8,8a-dimethyl-1,4,-4a,5,6,7,8,8a-octahydro-2-naphthalenyl]-1-ethanone (29).** To a stirred solution of LHMDS (1 M in THF, 0.44 mL, 0.44 mmol) at −78 °C was added a solution of **21** (22 mg, 0.11 mmol) in THF (0.3 mL). After stirred for 1 h at −78 °C, pyruvonitrile (152 mg, 2.20 mmol) was added, and stirred for another 10 min. The reaction mixture was quenched with 2 M NaOH at room temperature and stirred for 40 min. After neutralized with 2 M HCl, the mixture was extracted with Et_2O and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3:2) to give **29** (22.8 mg, 85%) as a colorless oil. IR (neat) ν 3417, 2933, 1668, 1620, 1418, 1309, 1241, 1030, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 7.2 Hz, 3H), 0.96 (s, 3H), 1.24−1.35 (m, 2H), 1.43−1.78 (m, 5H), 1.82 (d, J = 15.4 Hz, 1H), 2.03 (d, J = 18.4 Hz, 1H), 2.13 (s, 3H), 2.59 (dd, J = 6.6, 18.4 Hz, 1H), 2.66 (d, J = 15.4 Hz, 1H), 4.16 (ddd, J = 4.4, 4.8, 10.8 Hz, 1H), 15.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 25.1, 25.4, 28.0, 29.3, 32.2, 32.8, 33.7, 35.9, 43.5, 69.0, 104.4, 179.3, 199.9; MS (EI, 70 eV) *m*/*z* (% base peak) 238 (92), 223 (96), 205 (87), 181 (22), 137 (39), 108 (68), 81 (49), 43 (70), 18 (100); HRMS (EI) calcd for $C_{14}H_{22}O_3$ 238.1569, Found 238.1568.

(±)-Eremopetasidione (18). A mixture of **29** (5.7 mg, 0.024 mmol) and DDQ (22 mg, 0.096 mmol) in 1,4-dioxane (1 mL) was

stirred at room temperature for 48 h. The solvent was removed in vacuo, and the crude product was purified by silica-gel chromatography (hexane/EtOAc = 1:1) to give **18** (4.5 mg, 80%) as a colorless oil. IR (neat) ν 3443, 2934, 1689, 1681, 1595, 1357 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, J = 7.6 Hz, 3H), 1.29 (s, 3H), 1.31−1.40 (m, 1H), 1.53−1.63 (m, 3H), 1.71−1.79 (m, 1H), 1.92−1.99 (m, 1H), 2.05−2.11 (m, 1H), 2.38 (dd, J = 4.4, 17.2 Hz, 1H), 2.46 (s, 3H), 2.71 (dd, J = 4.4, 17.2 Hz, 1H), 3.69 (ddd, J = 4.4, 4.4, 8.8 Hz, 1H), 7.41 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 24.5, 26.3, 27.6, 30.8, 35.7, 40.7, 41.2, 44.1, 70.8, 136.8, 164.9, 196.7, 198.1; MS (EI, 70 eV) *m*/*z* (% base peak) 236 (22), 221 (17), 203 (12), 175 (10), 164 (100), 147 (12), 124 (21), 43 (56); HRMS (EI) calcd for $C_{14}H_{20}O_3$ 236.1412, Found 236.1414.

(4a*S,5*R**,6*S**,8a*R**)-4a,5-Dimethyl-6-(tetrahydro-2*H*-2-pyranyloxy)perhydro-2-naphthalenone (30).** To a stirred solution of **21** (123 mg, 0.63 mmol) in CH_2Cl_2 (6 mL) was added 3,4-dihydro-2*H*-pyran (106 mg, 1.26 mmol) and *p*TSA (3 mg). After stirred at room temperature for 10 min, the solvent was evaporated. The crude product was purified by silica-gel chromatography (hexane/EtOAc = 4:1) to give **30** (153 mg, 87%) as a colorless oil. IR (neat) ν 2941, 2871, 1716, 1451, 1200, 1114, 1025, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz, 3H), 1.19 (s, 3H), 1.20 (s, 3H), 1.10−2.00 (m, 26H), 2.20−2.50 (m, 10H), 3.46−3.51 (m, 2H), 3.86−3.93 (m, 4H), 4.62−4.68 (m, 2H); MS (EI, 70 eV) *m*/*z* (% base peak) 280 (M^+, 2), 196 (30), 179 (87), 161 (44), 121 (26), 85 (100), 67 (17), 55 (14), 41 (14); HRMS (EI) calcd for $C_{17}H_{28}O_3$ 280.2038, Found 280.2035.

(±)-3β-Hydroxyfuranoeremophilane (32). To a stirred solution of LHMDS (1 M in THF, 1.24 mL, 1.24 mmol) at −65 °C was added a solution of **30** (86 mg, 0.31 mmol) in THF (1.0 mL). After stirred for 1 h at −65 °C, a solution of $ZnCl_2$ (253 mg, 1.86 mmol) in THF (1.5 mL) was added, and it stirred for another 10 min. A solution of acetonyl tetrahydropyranyl ether (196 mg, 1.24 mmol) in THF (0.5 mL) was added to the reaction mixture and gradually raised to 5 °C over 1.5 h. After being stirred at 5 °C for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The aqueous solution was extracted with Et_2O and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/Et_2O = 2:3) to give **31** (94 mg, 70%) as a colorless oil. A mixture of **31** (94 mg, 0.214 mmol), THF (2 mL), H_2O (0.1 mL) and *p*TSA (4 mg) was heated to 70 °C for 3 h. After being cooled to room temperature, the mixture was quenched with saturated aqueous NH_4Cl. The aqueous solution was extracted with Et_2O and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4:1) to give **32** (34.7 mg, 69%) as a colorless oil. IR (neat) ν 3382, 2929, 2862, 1650, 1566, 1445, 1384, 1156, 1087, 1022, 791, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 0.97 (d, J = 7.6 Hz, 3H), 1.24−1.36 (m, 2H), 1.42−1.57 (m, 2H), 1.66−1.82 (m, 3H), 1.86 (d, J = 15.6 Hz, 1H), 1.89 (d, J = 1.2 Hz, 3H), 2.27 (d, J = 16.8 Hz, 1H), 2.64−2.74 (m, 2H), 4.18 (ddd, J = 4.8, 4.8, 13.2 Hz), 7.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.0, 8.1, 25.1, 26.5, 28.0, 29.0, 29.6, 34.5, 37.1, 44.3, 69.4, 115.0, 119.9, 137.2, 148.1; MS (EI, 70 eV) *m*/*z* (% base peak) 234 (M^+, 7), 210 (3), 189 (3), 162 (3), 137 (5), 108 (22), 88 (80), 70 (100), 61 (89); HRMS (EI) calcd for $C_{15}H_{22}O_2$ 234.1620, Found 234.1608.

(±)-3β-Angeloyloxyfuranoeremophilane (19). To a stirred solution of **32** (10 mg, 0.043 mmol) in CH_2Cl_2 (3 mL) at room temperature was added angeloyl chloride (51 mg, 0.43 mmol), and then it was stirred at room temperature for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 20:1) to afford **19** (8.2 mg, 61%) as a colorless oil. IR (neat) ν 2925, 2863, 1713, 1645, 1565, 1457, 1386, 1233, 1153, 1085, 1042, 986, 843, 794 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.72 (s, 3H), 0.91 (d, J = 7.2 Hz, 3H), 1.00−1.17 (m, 2H), 1.30−1.49 (m, 2H), 1.59−1.67 (m, 1H), 1.75 (s, 3H), 1.79 (d, J = 16.0 Hz, 1H), 1.88−1.95 (m, 1H), 1.91 (dq, J = 1.2, 1.2 Hz, 3H), 2.03 (dq, J = 1.2, 7.2 Hz, 3H), 2.13 (d, J = 16.8 Hz, 1H), 2.55 (dm, J = 16.8 Hz, 1H), 2.73 (d, J = 16.0 Hz, 1H), 5.44 (ddd, J = 4.4, 4.4, 12.4 Hz, 1H), 5.73 (qq, J = 1.2, 7.2 Hz, 1H), 7.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.1, 8.2, 15.7, 20.6, 24.9, 26.2, 26.5, 27.7, 29.0, 34.5, 37.2, 41.4, 72.3, 115.0, 120.0, 128.3, 137.2, 137.5, 147.9, 167.6; MS (EI, 70 eV) *m*/*z* (% base peak) 316 (M^+, 19), 233 (16), 216 (7), 159 (3), 120 (7), 108 (54), 83 (21), 32 (92), 28 (100); HRMS (EI) calcd for $C_{20}H_{28}O_3$ 316.2038, Found 316.2038.

(±)-3β-Methacryloyloxyfuranoeremophilane (20). To a stirred solution of **32** (26 mg, 0.111 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Et_3N (56 mg, 0.555 mmol) and methacryloyl chloride (35 mg, 0.333 mmol), and then it was stirred at 0 °C for 15 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2, The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 20:1) to afford **20** (21.8 mg, 65%) as a colorless oil. IR (neat) ν 2967, 2925, 2871, 1714, 1638, 1567, 1448, 1328, 1297, 1171, 1155, 1085, 984, 942, 794 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H), 1.32−1.54 (m, 2H), 1.60−1.79 (m, 2H), 1.82−1.98 (m, 3H), 1.90 (d, J = 1.2 Hz, 3H), 1.96 (s, 3H), 2.29 (d, J = 16.8 Hz, 1H), 2.69−2.79 (m, 2H), 5.31 (ddd, J = 4.4, 4.4, 12.4 Hz, 1H), 5.52−5.57 (m, 1H), 6.10−6.13 (m, 1H), 7.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.1, 8.2, 18.3, 24.9, 26.0, 26.5, 27.6, 29.0, 34.6, 37.2, 41.4, 72.8, 114.9, 120.0, 125.1, 136.9, 137.2, 147.9, 166.9; MS (EI, 70 eV) *m*/*z* (% base peak) 302 (M^+, 28), 233 (11), 216 (8), 159 (4), 120 (10), 108 (100), 91 (8), 69 (8); HRMS (EI) calcd for $C_{19}H_{26}O_3$ 302.1882, Found 302.1876.

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Supporting Information Available: General procedures and analytical data for all new compounds, copies of ^1H NMR for compounds **3**−**5a**, **5d**, **6e**−**8a**, **8d**, **9e**−**10**, **14**−**20**, **22**, **23**, **26b**, **29**, **30**, and **32**, as well as crystal structure and crystallographic file for **27**. This material is available free of charge via the Internet at http://pub.acs.org.

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