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Convergent Synthesis of Polycyclic Ethers via the Intramolecular Allylation of α-Acetoxy Ethers and Subsequent Ring-Closing Metathesis

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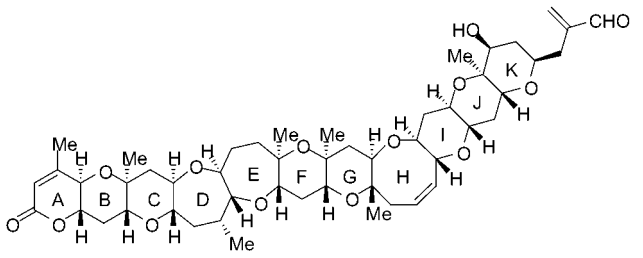
Abstract: The Lewis acid mediated reaction of α-acetoxy ethers **15**−**22** gave the corresponding cyclized products **23**, **25**, **27**, **29**, **31**, **32**, **34**, and **36** in good yields with high stereoselectivities. Those cyclized products were subjected to ring-closing metathesis to afford the polycyclic ethers **38**−**42**, **44**, and **45** in good yields. The usefulness of the present methodology was demonstrated by the convergent synthesis of the CDEF ring system of brevetoxin B (**1**) and the CDEFG ring system of gambierol (**2**).

Introduction

Since the discovery of brevetoxin B (**1**) in 1981,[1] a number of polycyclic ethers have been isolated from marine algae.[2] Due to their structural novelty and toxicity, those compounds are particularly attractive targets for synthetic chemists.[3−5] Gambierol (**2**), a potent neurotoxin isolated from the cultured cells of *Gambierdiscus toxicus*, has 8 ether rings and 18 stereogenic centers.[6] In the course of the synthetic study of **2**,[7,8] we encountered several difficult problems: for example, coupling of the E and H ring segments, involving the introduction of a methyl group on the G ring.[7d,f] Being faced with these problems, we needed to develop an efficient and reliable approach to the synthesis of polycyclic ether frameworks. Here, we wish to report a new methodology for the convergent synthesis of polycyclic ethers via the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis.[9]



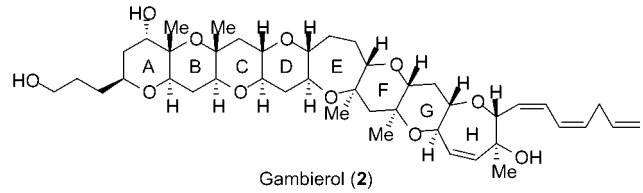


Figure 1.

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† Institute of Multidisciplinary Research for Advanced Materials.

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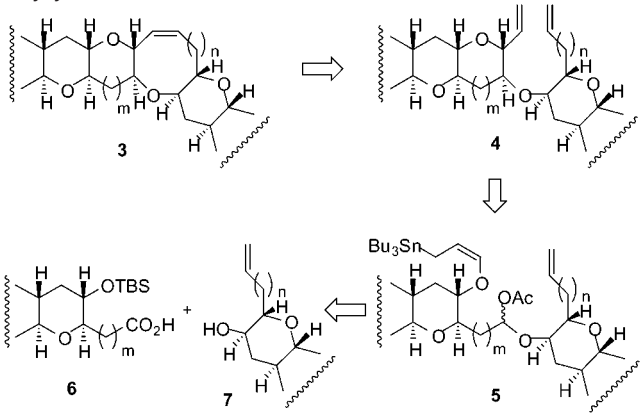
10.1021/ja025523g CCC: $22.00

Scheme 1. Synthetic Strategy for the Convergent Synthesis of Polycyclic Ethers

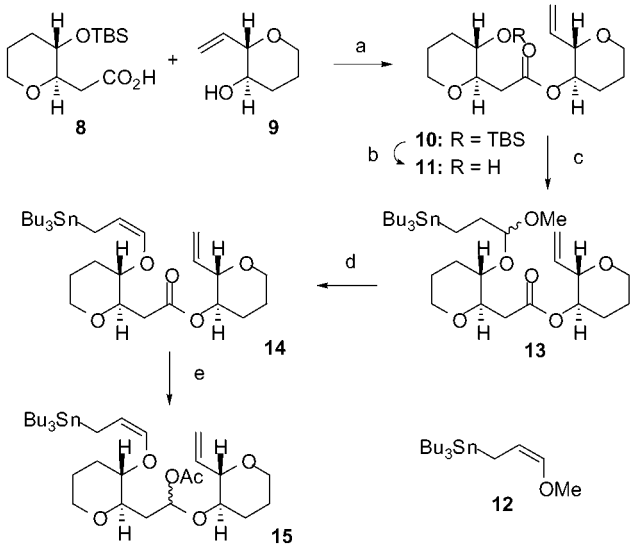


Results and Discussion

Scheme 1 illustrates our new synthetic strategy for the convergent synthesis of polycyclic ethers. Over the past few years, transition metal catalyzed ring-closing metathesis has been introduced and well recognized as a powerful tool for the synthesis of cyclic ethers.[10,11] Applying the *retro* ring-closing metathesis of **3** leads to the diene **4**. The crucial point of our strategy is the convergent synthesis of the key intermediate **4**. Recently, Rychnovsky and co-workers demonstrated the ability of α-acetoxy ethers as a substrate for the convergent synthesis of tetrahydropyran derivatives via Prins cyclization.[12] It was thought that the diene **4** would be synthesized from **5** via an intramolecular reaction of α-acetoxy ether and allylic stannane.[13−15] Retrosynthetic disassembly of **5** affords the carboxylic acid **6** and the alcohol **7**.

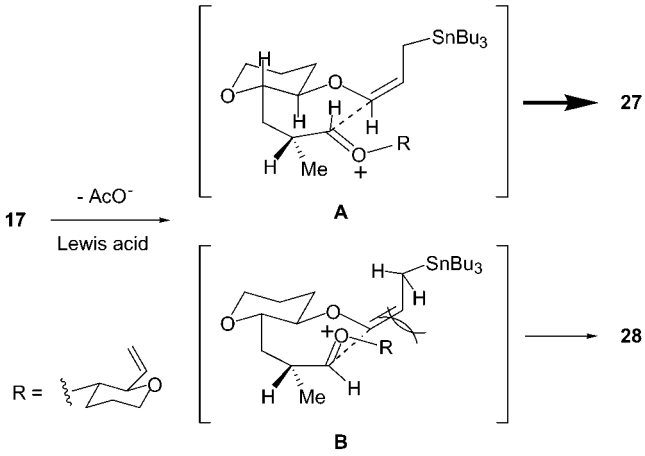
The synthesis of α-acetoxy ethers is rather straightforward and easy, and the synthesis of **15** is a representative (Scheme 2). The carboxylic acid **8**[16] and the alcohol **9**[17] were connected by DCC coupling to give the ester **10** in 90% yield. After deprotection of the silyloxy group, the alcohol **11** was converted to the allylic stannane **14** via the mixed acetal **13** in good yield.[18] The ester **14** was then subjected to the Rychnovsky protocol to give the α-acetoxy ether **15** as a mixture of diastereoisomers in 95% yield.[13,19]

Scheme 2[a]



[a] Reagents and conditions: (a) DCC, DMAP, CSA, CH_2Cl_2, room temperature, 90%; (b) TBAF, THF, room temperature, 100%; (c) **12**, CSA, CH_2Cl_2, room temperature, 95%; (d) TMSI, HMDS, CH_2Cl_2, −15 °C, 76%; (e) DIBALH, CH_2Cl_2, −78 °C, then Ac_2O, pyridine, DMAP, −78 °C to room temperature, 95%.

Scheme 3. Plausible Transition State Structures for the Reaction of **17**



The cyclization precursors **16**−**22** were prepared in a similar manner, and the results of the cyclization are summarized in Table 1. Treatment of **15** with 4 equiv of $BF_3{\cdot}OEt_2$ gave a 70:30 mixture of the cyclized products **23** and **24** in 79% yield (entry 1). The ^{1}H NMR spectrum of **23** was identical with that of the known compound.[11d] The stereochemistry of the minor isomer **24** was confirmed by ^{1}H NMR analysis and NOE experiments. Higher stereoselectivities were observed in the formation of seven-membered rings; the reactions of **16**−**19** with

(10) For a recent review of the synthesis of cyclic ethers via ring-closing metathesis, see: Yet, L. *Chem. Rev.* **2000**, 2963−3007.

(11) For the convergent synthesis of polycyclic ethers via ring-closing metathesis, see: (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565−1566. (b) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335−10336. (c) Oishi, T.; Nagumo, Y.; Hirama, M. *Synlett* **1997**, 980−982. (d) Oishi, T.; Nagumo, Y.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1998**, 1041−1042. (e) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337−1340. (f) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1999**, 1063−1064. (g) Oishi, T.; Nagumo, Y.; Shoji, M.; Brazidec, J.-Y. L.; Uehara, H.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1999**, 2035−2036. (h) Maruyama, M.; Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Heterocycles* **2001**, *54*, 93−99. (i) Oishi, T.; Uehara, H.; Nagumo, Y.; Shoji, M.; Brazidec, J.-Y. L.; Kosaka, M.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **2001**, 381−382.

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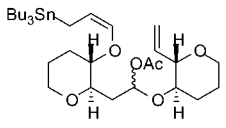
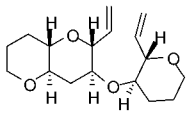
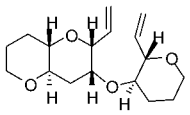
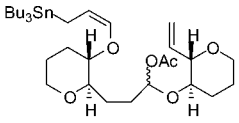
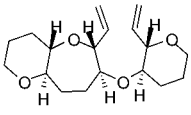
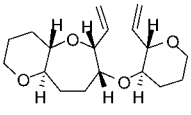
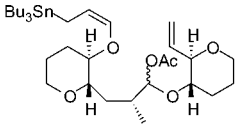
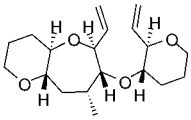
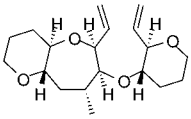
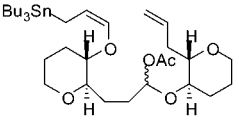
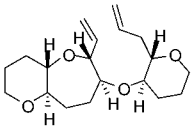
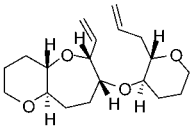
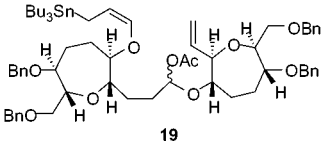
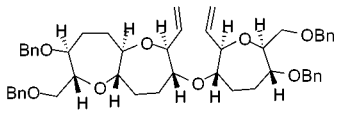
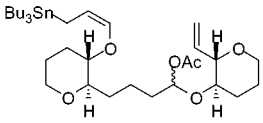
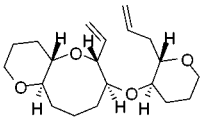
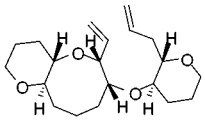
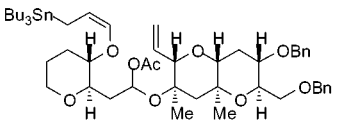
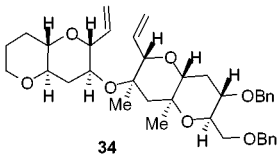
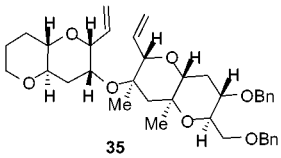
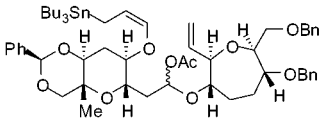
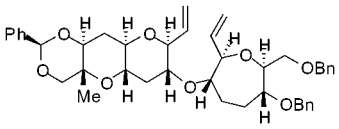
Table 1. Intramolecular Reaction of γ-Alkoxyallylstannane and α-Acetoxy Ether[a]

entry	substrate	products			yield[b]
1[c]	 **15**	 **23**	+ 70:30	 **24**	79%
2	 **16**	 **25**	+ >95:5	 **26**	73%
3	 **17**	 **27**	+ 82:18	 **28**	93%
4	 **18**	 **29**	+ 87:13	 **30**	67%
5	 **19**	 **31**			64%
6	 **20**	 **32**	+ >95:5	 **33**	60%
7	 **21**	 **34**	+ 71:29	 **35**	95%
8	 **22**	 **36**			74%

[a] Reactions were carried our with 4 equiv of $MgBr_2 \cdot OEt_2$ in the presence of molecular sieves 4A in CH_2Cl_2 at −20 °C. [b] Isolated yield. [c] $BF_3 \cdot OEt_2$ was used as a Lewis acid.

$MgBr_2 \cdot OEt_2$ afforded the corresponding cyclic ethers **25**, **27**, and **29**, respectively, as major products (entries 2−4).[20,21] It shoud be noted that the desired stereoisomer **27** was obtained predominantly from the reaction of **17**, which has a methyl substituent at the α-position of the acetoxy group. The stereoselectivity observed can be explained by the well-accepted acyclic transition state model (Scheme 3).[14c,22] The allylic stannane moiety is oriented to a *pseudo*-equatorial position to avoid the 1,3-diaxal repulsion in all cases, and the oxonium cation moiety, having a substituted tetahydropyranyl group R, also prefers a *pseudo*-equatorial position as depicted by the transition state structure **A**, which leads to the major product **27**. On the other hand, there is a significant steric repulsion between the tributylstanylmethyl and the R group in the transition state structure **B** giving the minor product **28**. Thus, the stereochemical outcome of this reaction is strongly dependent on the orientation of the allylic stannane moiety, rather than

(20) The use of $BF_3 \cdot OEt_2$ gave slightly lower yields.

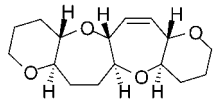
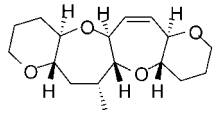
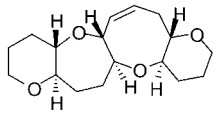
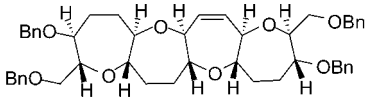
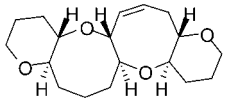
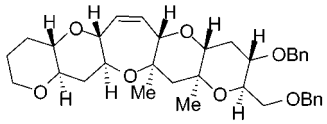
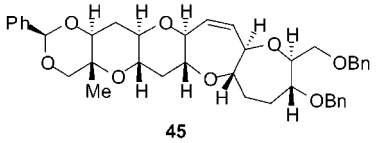
(21) Similar stereoselectivities were observed in the intramolecular reaction of allylic stannane and aldehyde giving six- and seven-membered cyclic ethers, see ref 13c.

(22) For recent reviews on the reaction of allylic stannanes, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Nishigaichi, Y.; Takuwa, A.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395−7426.

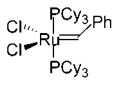
depending on the chirality at the α-position. This result is very promising and would allow us to synthesize the CDEF ring system of brevetoxin B (**1**) in a stereoselective and convergent manner. The reaction of the tetrabenzyl ether **19** gave **31** as the sole product in 64% yield (entry 5). The generality of this reaction is well demonstrated by the eight-membered ring formation. Thus, the reaction of **20** gave **32** in 60% yield with very high stereoselectivity (entry 6). In the total synthesis of **2**, one of the most difficult problems we had encountered was the introduction of two bridgehead methyl groups of the EFG ring. We examined several conceivable approaches to this problem, but all the attempts resulted in failure.[7f] However, **21** could be synthesized rather easily from the corresponding tertiary alcohol, and the cyclization with $MgBr_2 \cdot OEt_2$ gave a 71:29 mixture of **34** and **35** in 95% yield (entry 7). The relatively mild reaction conditions employed allowed the use of **22**, having an acetal protective group, as a substrate to give **36** in 74% yield with very high stereoselectivity (entry 8).

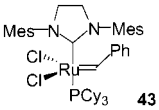
We next examined the ring-closing metathesis of the products **25**, **27**, **29**, **31**, **32**, **34**, and **36** (Table 2).[11,23] Treatment of **25** with Grubbs catalyst **37**[24] gave the tetracyclic ether **38** in 91% yield (entry 1). The reaction of **27** provided **39**, corresponding to the CDEF ring system of brevetoxin B (**1**), in 86% yield (entry 2). Similarly, the reactions of **29** and **31** proceeded smoothly to afford the tetracyclic ethers **40** and **41** in 64% and 84% yields, respectively (entries 3 and 4). Although the reaction of **32** with **37** gave **42** in 49% yield along with 28% of the starting material, the use of the more active catalyst **43** provided the 6,8,8,6-tetracyclic system **42** in 87% yield (entry 5).[25] Similarly, treatment of **36** with **43** provided the pentacyclic ether **45**, corresponding to the CDEFG ring system of gambierol (**2**), in 84% yield (entry 6). Although the reason is not clear, the reaction of **36** was very slow and afforded **45** in moderate yield (50%, entry 7)

Table 2. Ring-Closing Metathesis of the Dienes **25**, **27**, **29**, **31**, **32**, **34**, and **36**[a]

entry	substrate	product	yield[b]
1	**25**	 **38**	91%
2	**27**	 **39**	86%
3	**29**	 **40**	64%
4	**31**	 **41**	84%
5[c]	**32**	 **42**	87%
6[c]	**34**	 **44**	84%
7[c]	**36**	 **45**	50%

[a] Reactions were carried out with 20 mol % of **37** in CH_2Cl_2 at 35 °C. [b] Isolated yield. [c] Reactions were carried out with 20−40 mol % of **43** in CH_2Cl_2 at 35 °C.


37


43

Conclusion

We have developed an efficient and flexible method for the convergent synthesis of various polycyclic ethers via the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis. It should be noted that the use of an esterification reaction, one of the most common transformations in organic synthesis, for the segment coupling makes the present methodology reliable and practical (Scheme 2). Furthermore, the new method described here allows us to synthesize the CDEF ring segment of brevetoxin B (**1**) and the CDEFG ring segment of gambierol (**2**) in a convergent manner. Application of the present technology to the total synthesis of marine polycyclic ethers is in progress.

Experimental Section

General Procedure for the Intramolecular Allylation of α-Acetoxy Ethers. Synthesis of 23 and 24. To a mixture of **15** (21 mg, 0.033 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added $BF_3 \cdot OEt_2$ (0.2 M in CH_2Cl_2, 0.19 mL, 0.038 mmol). After being stirred for 1 h at −78 °C, the mixture was allowed to warm to −20 °C. The reaction was quenched with Et_3N. Concentration followed by silica gel column chromatography (hexane/EtOAc, 6:1 to 3:1) gave **23** (5.3 mg, 55%) and **24** (2.3 mg, 24%). **23**: colorless oil; R_f = 0.26 (hexane/EtOAc, 4:1); $[\alpha]^{25}_D$ +2.8° (*c* 1.55, $CHCl_3$); IR (neat) 2941, 1643, 1279, 1090 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) d 5.98 (ddd, *J* = 17.4, 10.6, 5.5 Hz, 1H), 5.93 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H), 5.42−5.28 (m, 2H), 5.26−5.16 (m, 2H), 3.86−3.97 (m, 2H), 3.63 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.56 (dd, *J* = 8.8, 5.5 Hz, 1H), 3.42−3.31 (m, 2H), 3.25 (ddd, *J* = 11.0, 9.3, 4.7 Hz, 1H), 3.18−2.91 (m, 3H), 2.36 (ddd, *J* = 11.6, 4.3, 4.3 Hz, 1H), 2.17−2.02 (m, 2H), 1.72−1.35 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 135.8, 117.7, 116.7, 81.3, 81.1, 77.5, 76.6, 76.5, 67.8,

(23) For recent reviews on ring-closing metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833−1835. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388.
(24) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.
(25) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

67.2, 37.8, 31.3, 29.2, 25.4, 25.2; HRMS (EI) calcd for $C_{17}H_{26}O_4$ (M^+) 294.1830, found 294.1812. **24**: colorless oil; $R_f = 0.16$ (hexane/EtOAc, 4:1); $[\alpha]^{24}_D$ −69.7° (*c* 0.85, $CHCl_3$); IR (neat) 2939, 1645, 1339, 1094 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.27 (ddd, $J = 17.4, 10.8, 5.2$ Hz, 1H), 6.02 (ddd, $J = 17.4, 10.6, 6.1$ Hz, 1H), 5.61 (ddd, $J = 17.4, 2.2, 1.5$ Hz, 1H), 5.32−5.19 (m, 2H), 5.08 (ddd, $J = 10.6, 2.0, 1.2$ Hz, 1H), 3.77−3.59 (m, 4H), 3.51 (ddd, $J = 11.6, 8.9, 4.4$ Hz, 1H), 3.19−2.95 (m, 4H), 2.88 (ddd, $J = 10.3, 9.0, 4.3$ Hz, 1H), 2.22 (ddd, $J = 13.0, 4.4, 2.9$ Hz, 1H), 2.01−1.91 (m, 1H), 1.84−1.73 (m, 1H), 1.55−1.04 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 136.1, 117.1, 117.1, 81.3, 80.9, 78.2, 77.2, 75.6, 74.2, 68.2, 67.4, 33.8, 29.7, 29.3, 25.8, 25.3; HRMS (EI) calcd for $C_{17}H_{26}O_4$ (M^+) 294.1830, found 294.1837.

General Procedure for the Ring-Closing Metathesis of Dienes: Synthesis of 38. To a mixture of **25** (73 mg, 0.24 mmol) in CH_2Cl_2 was added **37** (39 mg, 0.047 mmol). After being stirred for 20 h at 35 °C, the mixture was concentrated and purified by silica gel column chromatography (hexane/EtOAc, 6:1) to give **38** (60 mg, 91%): colorless needle; mp 102 °C (hexane); $R_f = 0.39$ (CH_2Cl_2/EtOAc, 10:1); $[\alpha]^{26}_D$ +26.4° (*c* 1.0, $CHCl_3$); IR (KBr) 2934, 1659, 1452, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddd, $J = 12.5, 2.9, 2.9$ Hz, 1H), 5.51 (ddd, $J = 12.5, 2.4, 2.4$ Hz, 1H), 4.07 (ddd, $J = 8.8, 4.8, 2.8$ Hz, 1H), 3.92−3.84 (m, 2H), 3.74 (ddd, $J = 9.0, 4.2, 2.2$ Hz, 1H), 3.53 (ddd, $J = 8.6, 4.3, 4.3$ Hz, 1H), 3.40−3.25 (m, 2H), 3.21−3.09 (m, 2H), 2.94 (ddd, $J = 9.1, 6.3, 6.3$ Hz, 1H), 2.13−1.80 (m, 6H), 1.74−1.59 (m, 4H), 1.55−1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 131.2, 84.2, 83.9, 83.8, 83.7, 81.3, 78.7, 68.0, 67.4, 31.5, 31.2, 31.1, 28.4, 26.0, 25.5; HRMS (EI) calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1678.

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Supporting Information Available: Complete experimental procedures and characterization data and ^1H NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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