Asymmetric Synthesis of the Diene Unit of Methyl Sartortuoate via a Temperature-Sensitive Intramolecular Horner–Wadsworth–Emmons (HWE) Reaction

Hequan Yao, Yuan Gao, Peng Liu, Bingfeng Sun, Xingxiang Xu*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: xuxx@mail.sioc.ac.cn

Received 15 November 2006

Abstract: The asymmetric synthesis of the diene unit of methyl sartortuoate is described. A temperature-sensitive intramolecular Horner–Wadsworth–Emmons reaction was employed for the construction of the 14-membered ring. A Payne rearrangement of an 2,3-epoxy alcohol was utilized for the installation of the hydroxyl group at the C14 position of the diene unit.

Key words: asymmetric synthesis, methyl sartortuoate, diene unit, HWE reaction, Payne rearrangement

Methyl sartortuoate (**1**) and methyl isosartortuoate (**2**), two representative members of the structurally novel class of biscembranoids, were isolated from the marine *Sarcophyton tortuosum tixierduriant* by Su et al. (Figure 1).[1,2] The relative configurations of **1** and **2** were elucidated by extensive NMR studies and their absolute stereochemistry was supported by X-ray analysis.[1] A preliminary bioassay proved that both of them displayed inhibitory effects against mice S180 and cytotoxic activities towards KB cells.[1] Biogenetically, **1** and **2** are proposed to be formed by a biosynthetic Diels–Alder reaction of two cembrenanes as the precursors. Although none of such precursors of **1** and **2** have been isolated, the hypothesis is supported by the isolation of methyl sarcoate (**4**),[2b] a dienophile unit of methyl sarcophytoate (**3**).[2a] While the potential bioactivity and the intriguing structural features as well as the interesting biogenetic possibility have aroused some synthetic interest, the total synthesis of these biscembranoids has not been reported to date. Nakata et al. has reported the elegant asymmetric synthesis of both the diene unit and the dienophile unit (i.e. **4**) of **3**.[3] Previously, we reported the asymmetric synthesis of the dienophile unit of **1** and **2**, and in this communication we describe the asymmetric synthesis of the diene unit (i.e. **5**) of **1**.[4]

Our initial retrosynthetic analysis of **5** is outlined in Scheme 1. We envisaged that the triene moiety of **5** could be derived from a triol **6**, which, in turn, would be achieved by opening of a 2,3-epoxy alcohol **7**. An intramolecular HWE reaction of an aldehyde phosphonoacetate **9** would be employed for the crucial cyclization to secure the 14-membered ring of **8**. Finally, **9** could be derived from a functionalized tetrahydropyran **10**.

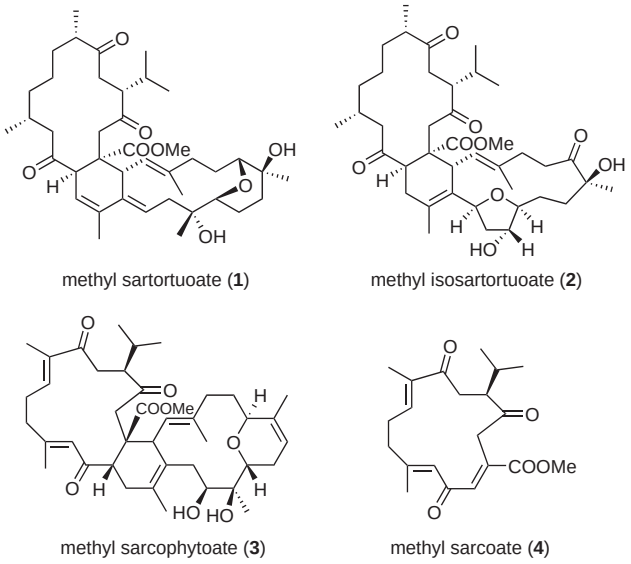
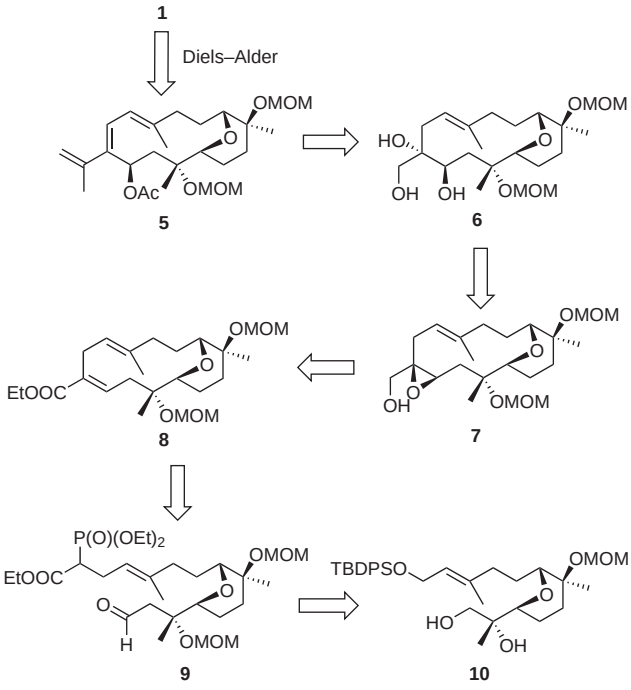


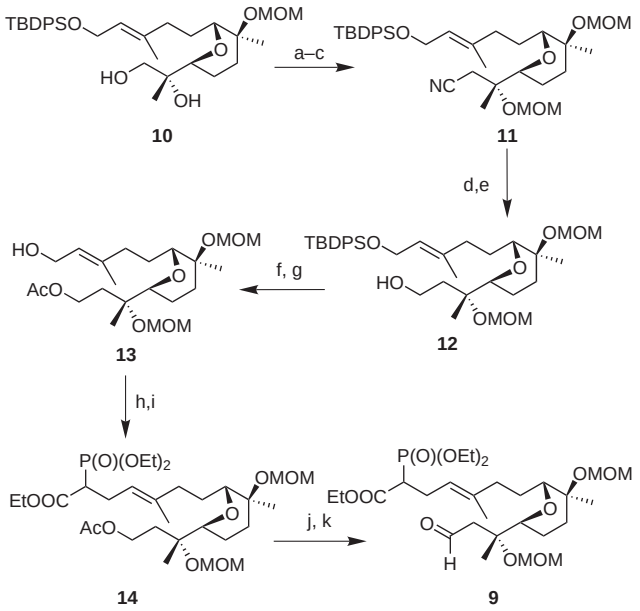
Figure 1 Selected biscembranoids **1**–**3** and methyl sarcoate (**4**)



Scheme 1 Retrosynthetic analysis of **5**

SYNLETT 2007, No. 4, pp 0571–0574
Advanced online publication: 21.02.2007
DOI: 10.1055/s-2007-967970; Art ID: W23006ST

The synthesis of the required precursor for the HWE reaction commenced with compound **10**, which has been prepared previously in our laboratory (Scheme 2).[4d] Thus, selective tosylation of the primary hydroxyl group of **10**, followed by treatment with KCN and protection of the tertiary alcohol with MOMCl provide the ether **11**.

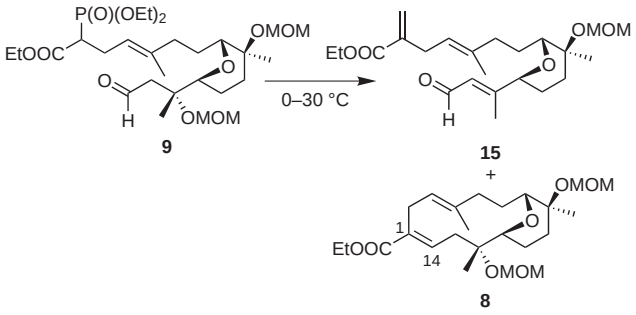


Scheme 2 *Reagents and conditions*: (a) TsCl, Et_3N, r.t., 95%; (b) KCN, EtOH–H_2O, 70 °C, 91%; (c) MOMCl, DIPEA, KI, CH_2Cl_2, 96%; (d) DIBAL-H, toluene, –78 °C, then HCl (1 M), 0 °C; (e) $NaBH_4$, MeOH, 0 °C, 73% for two steps; (f) Ac_2O, Et_3N, CH_2Cl_2, r.t., 96%; (g) TBAF, THF, r.t., 95%; (h) triphosgene, Et_3N, CH_2Cl_2, 0 °C; (i) $EtO_2CCH_2PO(OEt)_2$, NaH, DMSO, 0 °C to r.t.; (j) K_2CO_3, EtOH, r.t., 82% for three steps; (k) Dess–Martin periodiane, CH_2Cl_2, r.t., 92%.

Reduction of **11** with DIBAL-H, hydrolysis with 1 N HCl and further reduction with $NaBH_4$ afforded alcohol **12**. Acylation of the primary alcohol of **12** with Ac_2O and subsequent removal of the TBDPS group yielded the allylic alcohol **13**. Conversion of the hydroxyl group of **13** to the corresponding chloride followed by nucleophilic displacement with $EtO_2CCH_2PO(OEt)_2$ afforded **14**. Saponification of the acetyl group of **14** and oxidation of the resulting alcohol by Dess–Martin periodinane[5] afforded the desired aldehyde **9**.

With precursor **9** in hand, we then constructed the 14-membered ring using a HWE reaction.[6] We examined different reaction conditions and found that several typical conditions such as K_2CO_3–18-crown-6–toluene,[7] NaHMDS–THF[8] and LiHMDS–THF[8] gave a very complicated product mixture. When we tried the reaction using DBU–LiCl–MeCN,[9] **9** was transformed into an undesirable side product **15**[10] in 50% yield. The elimination of MOMO group under basic conditions produced MOMOH, which served as a carbon atom source for the intermolecular HWE reaction. Finally, the macrocyclization was successfully realized when we treated **9** with NaH and 18-crown-6 in DME. To optimize the macrocyclization conditions, we investigated the temperature effect. The results in Table 1 demonstrate that the reaction was temperature dependent. When the reaction was performed at 0 °C (entry 1), the desired product **8**[11] and the side product **15** were obtained in 1:1 ratio with moderate yield, whereas at 8–24 °C (entries 2–5), **8** became the major product and was obtained as a single *E*-isomer[12] at C1–C14. Surprisingly, when the reaction was performed at 30 °C, only the side product **15** was formed in this reaction (entry 6).

Table 1 Optimization of the Intramolecular HWE Reaction[a]

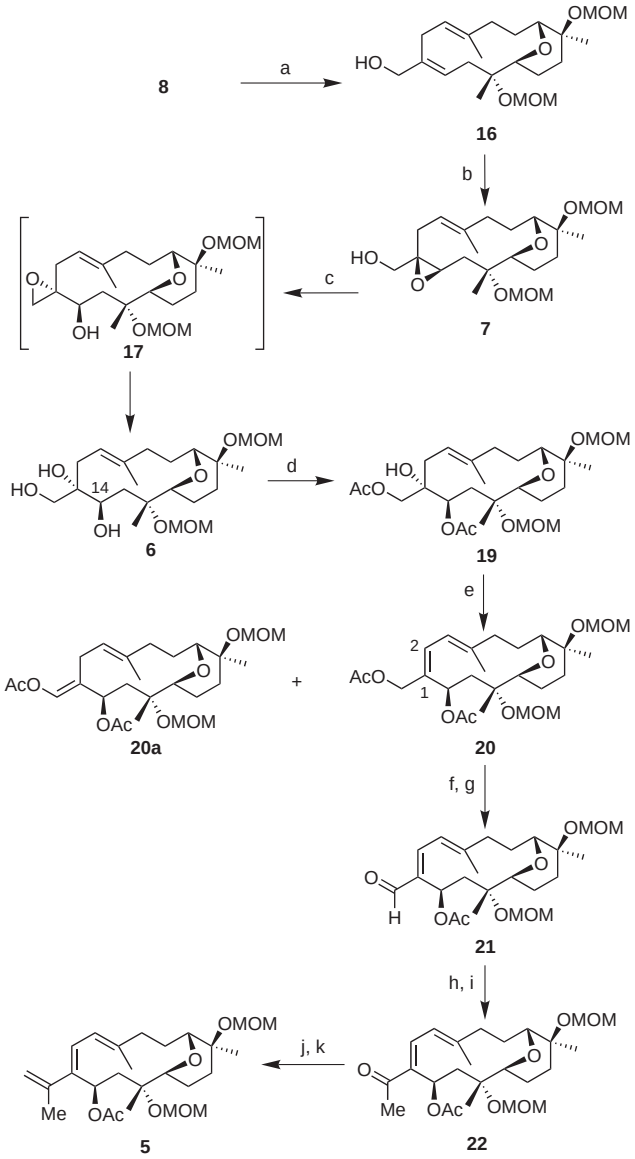


Entry	Temp (°C)	Yield (%) of **15**[b]	Yield (%) of **8**[b]	**15**/**8**
1	0	22	22	1:1
2	8	20	25	1:1.3
3	16	15	33	1:2.2
4	20	trace[c]	46	0:1
5	24	10	37	1:3.7
6	30	50	0	1:0

[a] Reactions were carried out in DME (0.003 M of **9**) using NaH (3.0 equiv) and 18-crown-6 (5 equiv) for 8 h.
[b] Isolated yield.
[c] Monitored by TLC.

Upon successful macrocyclization, we focused on the introducing the hydroxyl group at C14 and constructing the conjugated triene moiety (Scheme 3). Allylic alcohol **16**, which was obtained from the reduction of ester **8** with DIBAL-H, was epoxidized using Sharpless asymmetric epoxidation to get the epoxy alcohol **7**.[13] Initial attempts to open the epoxide of **7** to introduce 14-OH group utilizing Sharpless method[14] only afforded unreacted starting material. On the other hand, Payne rearrangement[15] of **7** followed by the in situ opening of the equilibrating 1,2-epoxide **17** with 0.5 M of NaOH in *t*-BuOH at 75 °C smoothly gave the triol **6** as a single isomer in 80% yield. Then, acylation of **6** with Ac_2O in pyridine, followed by elimination of tertiary alcohol using $SOCl_2$[16] provided a conjugated diene **20**[17] in 78% yield. X-ray analysis of this product confirmed the configurations of all stereocenters (Figure 2). To the best of our knowledge, this is the first example utilizing Payne rearrangement to introduce the hydroxyl group at 14-position of cembranoids. The elim-

ination of the tertiary alcohol of **19** gave **20** and unconjugated diene **20a** in a 5:1 ratio. Compounds **20** and **20a** could be separated by standard chromatographic methods. The acetyl group of **20** was then removed with K_2CO_3 in EtOH at 0 °C and the resulting alcohol was oxidized with Dess–Martin oxidation to afford aldehyde **21**. Treatment of **21** with MeMgBr, followed by oxidation yielded ketone **22**.[18] Due to the poor reactivity of the unsaturated ketone, methylenation of **22** failed under several conditions, such as Lombardo's conditions,[19] Takai's conditions[20] and Petasis's conditions.[21] Fortunately, treatment of **22** with MeMgBr, followed by dehydration using MsCl and Et_3N smoothly afforded the desired triene unit **5**.[22]



Scheme 3 *Reagents and conditions*: (a) DIBAL-H, Et_2O, –78 °C, 95%; (b) *tert*-butyl hydroperoxide (TBHP), D-(–)-DIPT, CH_2Cl_2, –20 °C, 77%; (c) 0.5 M NaOH, *t*-BuOH, H_2O, r.t. to 75 °C, 63%; (d) Ac_2O, pyridine, r.t., 90%; (e) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 78%; (f) K_2CO_3, EtOH, 0 °C, 66%; (g) Dess–Martin periodiane, CH_2Cl_2, r.t., 53%; (h) MeMgBr, THF, –78 °C; (i) Dess–Martin periodiane, $NaHCO_3$, CH_2Cl_2, r.t., 36% for two steps; (j) MeMgBr, THF, –20 °C; (k) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 33% for two steps.

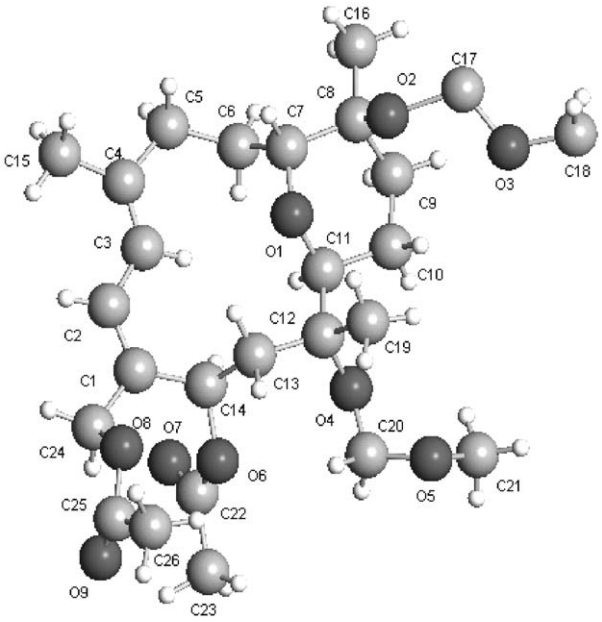


Figure 2 X-ray crystal structure of **20**

In summary, the asymmetric synthesis of the diene unit of **1** has been successfully achieved. Key steps were the temperature-sensitive intramolecular HWE reaction for the construction of the 14-membered ring and Payne rearrangement of 2,3-epoxyl alcohol for the installation of the hydroxyl group at the 14-position of the diene unit. Efforts towards the total synthesis of **1** by a Diels–Alder reaction are still in progress.

Acknowledgment

This work was supported by Chinese Academy of Sciences and the National Natural Science Foundation of China.

References and Notes

(1) (a) Su, J.; Long, K.; Peng, T.; Zheng, Q.; Lin, X. *Acta Chim. Sin.* **1985**, *43*, 796. (b) Su, J.; Long, K.; Peng, T.; Zeng, L.; Zheng, Q.; Lin, X. *Sci. Sin., Ser. B (Engl. Ed.)* **1988**, *31*, 1172. (c) Su, J.; Long, K.; Peng, T.; He, C. H.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 177.

(2) For other related compounds, see: (a) Kusumi, T.; Igari, M.; Ishitsuka, M. O.; Itezono, Y.; Nakayama, N.; Kakisawa, H. *J. Org. Chem.* **1990**, *55*, 6286. (b) Leone, P. A.; Bowden, B. F.; Carrol, A. R.; Coll, J. C.; Meehan, G. V. *J. Nat. Prod.* **1993**, *56*, 521. (c) Zeng, L.; Lan, W.; Su, J.; Zhang, G.; Feng, X.; Liang, Y.; Yang, X. *J. Nat. Prod.* **2004**, *67*, 1915. (d) Feller, M.; Rudi, A.; Berer, N.; Goldberg, I.; Stein, Z.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *J. Nat. Prod.* **2004**, *67*, 1303. (e) Ishitsuka, M. O.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2917.

(3) For synthetic studies on biscembranoids by the Nakata's group, see: (a) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Synlett* **1997**, 899. (b) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1417. (c) Ichige, T.; Kamimura, S.; Mayumi, K.; Sakamoto, Y.; Terashita, S.; Ohteki, E.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2005**, *46*, 1263.

(4) (a) Chen, X.; Fan, C.; Xu, X. *Chin. J. Chem.* **2000**, *18*, 717. (b) Hong, Z.; Chen, X.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 485. (c) Hong, Z.; Chen, X.; Xu, X. *Tetrahedron Lett.* **2003**, *44*, 489. (d) Gao, Y.; Nan, F.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4811. (e) Liao, X.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4641. (f) Liu, P.; Liao, X.; Xu, X. *Chin. J. Chem.* **2003**, *21*, 811. (g) Liu, P.; Xu, X. *Tetrahedron Lett.* **2004**, *45*, 5163.

(5) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(6) (a) Marynoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.

(7) (a) Paquette, L. A.; Wang, T. Z.; Philippo, C.; Wang, S. P. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030.

(8) Stock, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010.

(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Saka, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(10) **Compound 15**: colorless oil; $[\alpha]_D^{20}$ +15.8 (*c* = 0.50, MeOH). IR (film): 2932, 1717, 1676, 1448, 1184, 1137, 1098, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.09 (d, *J* = 7.8 Hz, 1 H), 6.14 (s, 1 H), 6.12 (d, *J* = 7.8 Hz, 1 H), 5.39 (s, 1 H), 5.22 (t, *J* = 7.5 Hz, 1 H), 4.77 (d, *J* = 7.2 Hz, 1 H), 4.72 (d, *J* = 7.2 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 4.08–4.11 (m, 1 H), 3.62–3.66 (m, 1 H), 3.39 (s, 3 H), 3.01 (d, *J* = 7.5 Hz, 2 H), 2.19 (s, 3 H), 1.40–2.10 (m, 8 H), 1.64 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.20 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.7, 167.3, 161.6, 139.7, 137.2, 126.2, 124.4, 120.8, 90.7, 77.8, 74.8, 72.67, 60.6, 55.5, 36.0, 31.5, 30.1, 26.5, 24.6, 21.0, 16.1, 14.3, 14.2. ESI–MS: *m*/*z* = 409.1 $[M + H]^+$, 431.1 $[M + Na]^+$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{36}O_6$: 431.2404; found: 431.2401.

(11) **Compound 8**: colorless oil; $[\alpha]_D^{20}$ +88.4 (*c* = 0.49, $CHCl_3$). IR (film): 2979, 2934, 1707, 1448, 1380, 1222, 1145, 1097, 1037, 919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.81 (t, *J* = 7.2 Hz, 1 H), 5.36 (t, *J* = 7.5 Hz, 1 H), 4.82 (d, *J* = 8.1 Hz, 1 H), 4.77 (d, *J* = 7.5 Hz, 1 H), 4.75 (d, *J* = 7.5 Hz, 1 H), 4.73 (d, *J* = 8.1 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.76–3.80 (m, 1 H), 3.69 (d, *J* = 5.1 Hz, 1 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 2.70–3.10 (m, 4 H), 2.32–2.40 (m, 1 H), 2.00–2.10 (m, 2 H), 1.80–2.00 (m, 2 H), 1.50–1.70 (m, 3 H), 1.62 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.25 (s, 3 H), 1.19 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 142.0, 139.1, 127.8, 123.2, 91.4, 90.9, 79.6, 77.4, 76.4, 75.9, 60.0, 55.6, 55.4, 39.7, 38.4, 33.9, 29.5, 27.7, 23.6, 22.7, 21.4, 15.4, 14.3. ESI–MS: *m*/*z* = 463.2 $[M + Na]^+$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{40}O_7$: 463.2666; found: 463.2685.

(12) The stereochemistry of the conjugated double bond is assigned from the chemical shift and the coupling constant data of the vinylic proton, and by analogy with closely related cyclizations.

(13) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(14) (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(15) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(16) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947.

(17) (a) **Compound 20**: white solid; mp 80–81 °C; $[\alpha]_D^{20}$ –234 (*c* = 0.40, $CHCl_3$). IR (film): 2942, 1740, 1376, 1243, 1092, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.27 (d, *J* = 10.5 Hz, 1 H), 6.05 (dd, *J* = 8.4 Hz, 2 H), 4.22 (d, *J* = 7.5 Hz, 1 H), 4.83 (d, *J* = 7.5 Hz, 1 H), 4.71 (d, *J* = 7.5 Hz, 1 H), 4.65 (d, *J* = 12.3 Hz, 1 H), 4.37 (d, *J* = 12.3 Hz, 1 H), 4.92 (d, *J* = 7.5 Hz, 1 H), 3.97–4.01 (m, 1 H), 3.73 (d, *J* = 8.4 Hz, 1 H), 3.40 (s, 3 H), 3.32 (s, 3 H), 2.50–2.62 (m, 1 H), 2.15–2.33 (m, 1 H), 2.14–2.15 (m, 8 H), 2.054 (s, 3 H), 2.047 (s, 3 H), 1.74 (s, 3 H), 1.23 (s, 3 H), 1.21 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.1, 139.0, 134.6, 126.0, 118.1, 91.0, 90.8, 82.7, 79.9, 75.2, 69.0, 68.4, 65.2, 55.7, 55.2, 40.4, 39.8, 30.3, 24.6, 21.1 (2 C), 21.0, 20.0, 19.9, 18.3. ESI–MS: *m*/*z* = 521.3 $[M + Na]^+$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{42}O_9$: 521.2721; found: 521.2743. (b) The crystallographic data for **20** has been deposited at the Cambridge Crystallographic Data Centre with deposition no. CCDC 632316.

(18) **Compound 22**: colorless oil; $[\alpha]_D^{20}$ –254 (*c* = 0.10, $CHCl_3$). IR (film): 2981, 2945, 2855, 1734, 1673, 1647, 1440, 1376, 1275, 1244, 1033, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 10.2Hz, 1 H), 6.25 (d, *J* = 11.1 Hz, 1 H), 5.95 (d, *J* = 10.2 Hz, 1 H), 5.03 (d, *J* = 7.2 Hz, 1 H), 4.82 (d, *J* = 7.5 Hz, 1 H), 4.69 (d, *J* = 7.5 Hz, 1 H), 4.42 (d, *J* = 7.2 Hz, 1 H), 3.98–4.02 (m, 1 H), 3.70–3.73 (m, 1 H), 3.40 (s, 3 H), 3.33 (s, 3 H), 1.80–2.70 (m, 4 H), 2.27 (s, 3 H), 2.00 (s, 3 H), 1.40–1.80 (m, 6 H), 1.83 (s, 3 H), 1.23 (s, 3 H), 1.20 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.2, 170.6, 145.2, 140.7, 131.9, 118.3, 91.1, 91.0, 82.5, 80.1, 75.2, 68.5, 68.4, 55.7, 55.3, 40.2, 39.6, 30.1, 27.5, 24.5, 21.3, 21.0, 20.1, 20.0, 18.8. ESI–MS: *m*/*z* = 491.1 $[M + Na^+]$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{40}O_8$: 491.2615; found: 491.2605.

(19) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.

(20) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

(21) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(22) **Compound 5**: colorless oil; $[\alpha]_D^{20}$ –176 (*c* = 0.05, $CHCl_3$). IR (film): 2925, 2853, 1742, 1458, 1375, 1240, 1144, 1092, 1072, 1034, 910 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.08–6.13 (m, 3 H), 4.96 (d, *J* = 7.4 Hz, 1 H), 4.93 (s, 1 H), 4.85 (s, 1 H), 4.84 (d, *J* = 7.3 Hz, 1 H), 5.03 (d, *J* = 7.3 Hz, 1 H), 4.39 (d, *J* = 7.4 Hz, 1 H), 4.03 (dd, *J* = 3.0 Hz, 1 H), 3.69 (d, *J* = 8.3 Hz, 1 H), 3.40 (s, 3 H), 3.33 (s, 3 H), 1.40–2.80 (m, 10 H), 1.98 (s, 3 H), 1.88 (s, 3 H), 1.73 (s, 3 H), 1.25 (s, 3 H), 1.21 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 143.5, 137.4, 121.2, 119.0, 113.9, 112.9, 91.1, 91.0, 82.7, 80.2, 75.3, 69.8, 68.3, 55.7, 55.2, 40.3, 39.8, 30.4, 29.7, 24.6, 22.8, 21.5, 21.1, 20.2, 18.4. ESI–MS: *m*/*z* = 489.4 $[M + Na]^+$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{42}O_7$: 489.2828; found: 489.2823.