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# Synthesis of the C1–C16 fragment of spirastrellolide A

Jia Liu, Jin Haek Yang, Changhong Ko and Richard P. Hsung*

*Division of Pharmaceutical Sciences and Department of Chemistry, 777 Highland Avenue, University of Wisconsin, Madison, WI 53705, United States*

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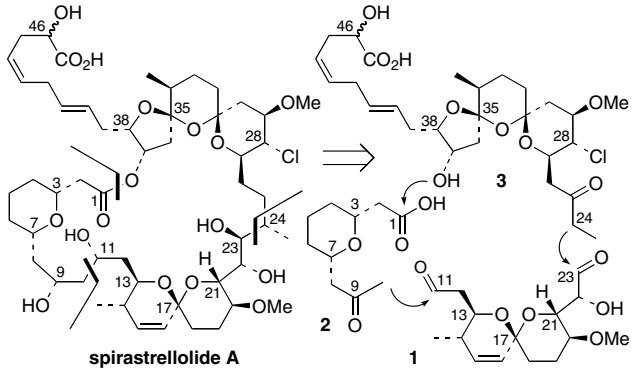
**Abstract**—Synthesis of the C1–C16 fragment of spirastrellolide A is described here featuring Sharpless asymmetric epoxidation, an acid promoted *O*-1,4-addition, and Mukaiyama 1,3-*anti*-aldol.

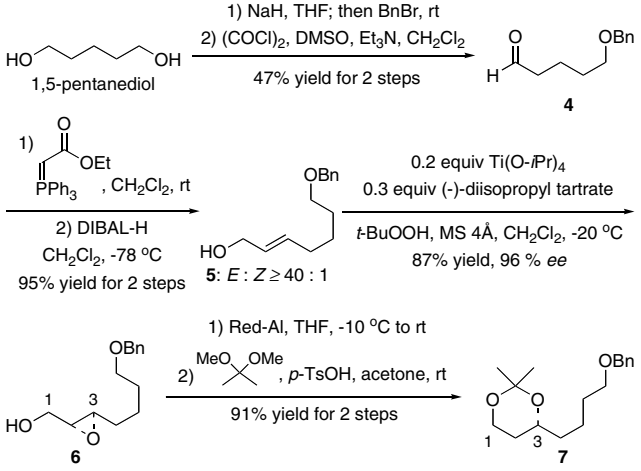

We have been working toward a total synthesis of spirastrellolide A, a spiroketal-rich macrolide found recently from marine sponge *Spirastrellolide coccinea* (Scheme 1).[1] In addition to its ability to cause untimely mitotic arrest in cells, spirastrellolide A was shown to exhibit potent inhibitory activity against protein phosphatase 2A [$IC_{50} = 1$ nM] with an impressive selectivity for PP2A over PP1 [ratio of $IC_{50}$ values = 1:50].[1,2] Given its biological relevance in cancer therapeutic development, and it structural challenge, spirastrellolide A has already attracted attentions from the synthetic community.[3] Retrosynthetically, we planned to approach spirastrellolide A via connecting three major fragments: spiroketal **1**, pyran **2**, and trioxadispiroketal **3**. Recently, we communicated[4] our synthesis of the C11–*epi*-C22–C23 fragment (see **1**) as a proof-of-concept application to feature a ketal-tethered RCM strategy[5] for constructing of spiroketals.[6] We report here our synthesis of C1–C16 fragment.




Scheme 1.

Our synthesis commenced with 1,5-pentanediol, which was quickly transformed into aldehyde **4**[7] in 47% overall yield via mono-benzylation and Swern oxidation[8] (Scheme 2). HEW-Modified Wittig olefination,[9] followed by Dibal-H reduction, sets up the key allyl alcohol **5** in 95% overall yield exclusively as an *E*-isomer. Sharpless asymmetric epoxidation[10,11] employing D-(−)-diisopropyl tartrate provided epoxy alcohol **6** in 96% ee,[12] thereby establishing the key C3 stereocenter.

It is noteworthy that we have provided here an alternative approach for establishing the C3 stereochemistry in




Scheme 2.

* Corresponding author. Tel.: +1 608 890 1063; fax: +1 608 262 5345; e-mail: rhsung@wisc.edu

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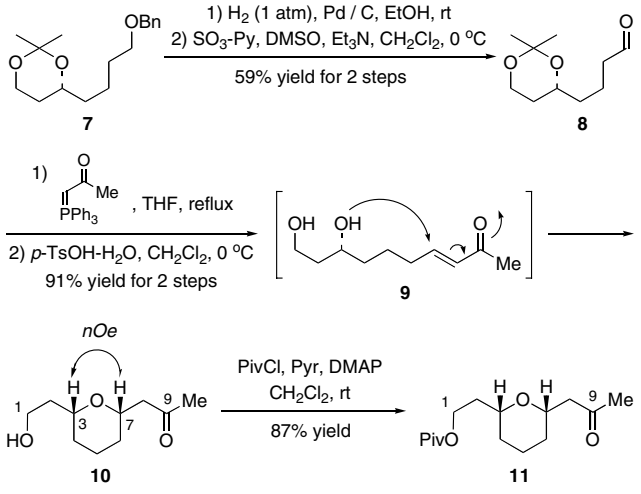
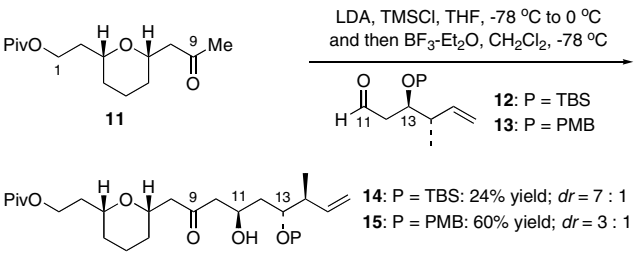
spirastrellolide A, as both Paterson[3a–c] and De Brabander[3d] employed an asymmetric Brown-allylation. A directed-reductive ring-opening of the epoxide proceeded regioselectively and a subsequent diol protection using 2,2-dimethoxy propane gave acetonide **7**.

With the optically enriched acetonide **7** in hand, we proceeded to complete the pyran synthesis. As shown in Scheme 3, debenzylation followed by a modified-Moffat oxidation[13] gave aldehyde **8**. Wittig olefination and subsequent hydrolysis of the acetonide group occurred concomitantly with the pyran formation through a thermodynamically controlled intramolecular *O*-1,4-addition to afford **10** in 91% overall yield, thereby completing the synthesis of C1-10 fragment of spirastrellolide A. The relative *syn* relationship at C3 and C7 was confirmed through NOE. Ensuing protection of the C-1 alcohol in **10** gave the pivaloyl protected methyl ketone **11**, which is suitable for a potential C10–C11 connection as proposed in Scheme 1.

To examine the concept of connecting C10 and C11 through a diastereoselective aldol addition, we prepared aldehyde **12** and **13**.[14,15] As shown in Scheme 4, by employing Mukaiyama's conditions,[16] methyl ketone **11** was first converted to its respective TMS enol ether using LDA and TMSCl, and the resulting TMS enol ether intermediate was added to aldehyde **12** or **13**, followed by the addition of a stoichiometric amount of $BF_3$–$Et_2O$ at −78 °C to give the aldol product **14** in 24% yield with a diastereomeric ratio of about 7:1 with the major isomer assigned as the desired 1,3-*anti* product based on Evans' non-chelation 1,3-asymmetric induction model.[17] By using aldehyde **13** under the same conditions, the yield for the respective aldol product **15** was much improved but the ratio was 3:1. On the other hand, by following Evans boron enolate conditions,[18] addition of the di-*n*-butylboron enolate [not shown] derived from methyl ketone **11** with aldehyde **12** in $CH_2Cl_2$ at −78 °C afforded **14** with 29% yield but in ~1:1 ratio.




**Scheme 3.**




**Scheme 4.**

We have described here a concise synthesis C1-10 pyranyl unit that differed from the existing syntheses of comparable fragment in spirastrellolide A. We have also demonstrated the feasibility of connecting C10 and C11 through a selective Mukaiyama-type aldol addition, thereby constituting a synthesis of the C1-16 fragment. Efforts are under way in completing the total synthesis of spirastrellolide A.

## Acknowledgments

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## References and notes

1. (a) William, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. *J. Am. Chem. Soc.* **2003**, *125*, 5296; (b) William, D. E.; Lapawa, M.; Feng, X.; Tarling, T.; Roberge, M.; Andersen, R. *Org. Lett.* **2004**, *6*, 2607.
2. Roberge, M.; Cinel, B.; Anderson, H. J.; Lim, L.; Jiang, X.; Xu, L.; Kelly, M. T.; Andersen, R. J. *Cancer Res.* **2000**, *60*, 5052.
3. (a) Paterson, I.; Anderson, E. A.; Dalby, S. M. *Synthesis* **2005**, 3225; (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4121; (c) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125; (d) Pan, Y.; De Brabander, J. K. *Synlett* **2006**, 853; (e) Wang, C.; Forsyth, C. J., Abstract No. ORGN-414, 229th ACS National Meeting, San Diego, CA, Spring, 2005.
4. Liu, J.; Hsung, R. P. *Org. Lett.* **2005**, *6*, 2273.
5. (a) Ghosh, S. K.; Hsung, R. P.; Liu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8260; (b) Ghosh, S. K.; Hsung, R. P.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 5505; (c) Wang, J.; Hsung, R. P.; Ghosh, S. K. *Org. Lett.* **2004**, *6*, 1939.
6. For a review on chemistry of spiroketals, see: (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227; (b) Brimble, M. A.; Fares, F. A. *Tetrahedron* **1999**, *55*, 7661; (c) Fletcher, M. T.; Kitching, W. *Chem. Rev.* **1995**, *95*, 789; (d) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.
7. Selected characterizations of new compounds. Compound **5**: $R_f = 0.35$ [33% EtOAc/hexane]; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.44–1.51 (m, 2H), 1.60–1.67 (m, 2H), 1.80 (s, 1H), 2.04–2.09 (q, $J = 7.2$ Hz, 2H), 3.47 (t, $J = 6.4$ Hz, 2H), 4.08 (d, $J = 7.2$ Hz, 2H), 4.50 (s, 2H), 5.60–5.73 (m, 2H), 7.25–7.37 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 26.0, 29.5, 32.2, 63.8, 70.4, 73.1, 127.8, 127.9, 127.9, 128.6, 128.6, 129.6, 132.9, 138.8; IR (neat) cm$^{-1}$; 3393br s, 2934s, 2858s, 2361s, 1455s, 1363s. Compound **6**: $R_f = 0.10$ [30% EtOAc

in hexanes]; $[\alpha]_D^{23}$ 36.6 [$c = 0.89$, $CH_2Cl_2$]; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.54–1.65 (m, 2H), 1.61–1.69 (m, 1H), 1.86 (br s, 1H), 2.91 (dt, $J = 4.0$, 2.5 Hz, 1H), 3.50 (dt, $J = 2.5$, 5.5 Hz, 1H), 3.49 (t, $J = 6.5$ Hz, 2H), 3.62 (ddd, $J = 4.5$, 7.0, 11.5 Hz, 1H), 3.89 (ddd, $J = 2.5$, 5.5, 13.0 Hz, 1H), 4.51 (s, 2H), 7.28–7.30 (m, 1H), 7.30–7.35 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 22.7, 29.5, 31.4, 56.0, 58.7, 61.9, 70.1, 72.9, 127.6, 127.7, 128.4, 138.5; IR (neat) $cm^{-1}$ 3434br s, 3030m, 2936s, 2861m, 1100s; mass spectrum (APCI): *m/e* (% relative intensity) 237.2 $(M+H)^+$ (100). Compound **7**: $R_f = 0.35$ [17% EtOAc/hexane]; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (s, 3H), 1.38–1.43 (m, 2H), 1.44 (s, 3H), 1.46–1.58 (m, 4H), 1.63 (tt, $J = 6.8$, 6.8 Hz, 2H), 3.47 (t, $J = 6.8$ Hz, 2H), 3.82 (ddd, $J = 1.6$, 5.2, 12.0 Hz, 2H), 3.95 (td, $J = 2.8$, 12.4 Hz, 1H), 4.54 (s, 2H), 7.26–7.37 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 19.5, 21.8, 29.9, 30.3, 31.5, 36.5, 60.3, 69.0, 70.5, 73.1, 98.4, 127.7, 127.9, 127.9, 128.6, 128.6, 138.9; IR (neat) $cm^{-1}$ 2992s, 2940s, 2862s, 2360s. Compound **8**: $R_f = 0.45$ [33% EtOAc/hexane]; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (s, 3H), 1.39–1.44 (m, 1H), 1.45 (s, 3H), 1.47–1.83 (m, 5H), 2.46 (td, $J = 1.6$, 6.4 Hz, 2H), 3.81–3.88 (m, 2H), 3.93–3.99 (td, $J = 2.8$, 12.0 Hz, 1H), 9.77 (t, $J = 1.6$ Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 18.0, 19.5, 30.2, 31.5, 36.0, 44.0, 60.2, 68.8, 98.5, 202.8; IR (neat) $cm^{-1}$ 3300m, 2993s, 2938s, 2869s, 1718s. Compound **10**: $R_f = 0.33$ [67% EtOAc/hexane]; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.17–1.35 (m, 2H), 1.51–1.65 (m, 3H), 1.66–1.76 (m, 1H), 1.81–1.87 (m. 1H), 2.16 (s, 3H), 2.47 (dd, $J = 4.8$, 16.0 Hz, 1H), 2.57 (br s, 1H), 2.67 (dd, $J = 7.6$, 16.0 Hz, 1H), 3.60 (dddd, $J = 2.0$, 3.6, 8.4, 12.8 Hz, 1H), 3.76 (dt, $J = 5.6$, 5.6 Hz, 2H), 3.83 (dddd, $J = 2.0$, 4.8, 8.0, 12.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 23.5, 31.1, 31.3, 31.4, 38.2, 50.3, 61.5, 74.2, 78.5, 207.5; IR (neat) $cm^{-1}$; 3852m, 3675m, 3649m, 3629m, 3376br s, 2934s, 2860s, 2340s, 1716s, 1670s; mass spectrum (APCI): *m/e* (% relative intensity) 187 (M+H, 100), 169 (24), 151(27), 129(84), 111(18). Compound **11**: $R_f = 0.40$ [25% EtOAc/hexane]; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.19 (s, 9H), 1.53–1.63 (m, 2H), 1.53–1.63 (m, 3H), 1.75 (dd, $J = 7.0$, 13.0 Hz), 1.82–1.85 (m, 1H), 2.18 (s, 3H), 2.41 (dd, $J = 5.0$, 15.0 Hz, 1H), 2.66 (dd, $J = 7.5$, 15.0 Hz, 1H), 3.42 (dddd, $J = 1.5$, 7.0, 10.5, 13.0 Hz, 1H), 3.75 (dddd, $J = 2.0$, 5.0, 8.0, 11.0 Hz, 1H), 4.12 (ddd, $J = 6.0$, 10.5, 11.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 23.7, 27.4, 27.4, 27.4, 31.2, 31.5, 31.6, 35.6, 39.0, 50.6, 61.3, 74.7, 74.8, 178.7, 207.8; IR (neat) $cm^{-1}$ 3420br s, 2929s, 2857s, 2360s, 2341s 1710s; mass spectrum (APCI): *m/e* (% relative intensity) 293 $(M+Na^+)$ (14), 271 (M+H) (100), 253 (71), 213 (85), 169 (50), 151 (89), 133 (19), 129 (6), 111 (42). Compound **12**: $R_f = 0.80$ [30% EtOAc in hexanes]; $[\alpha]_D^{23}$ 4.35 [*c* 0.96, $CHCl_3$]; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.040 (s, 3H), 0.052 (s, 3H), 0.89 (s, 9H), 1.00 (d, $J = 7.0$ Hz, 3H), 1.62–1.72 (m, 2H), 2.29 (dddd, $J = 4.0$, 7.0, 7.0, 14.0 Hz, 1H), 3.45–3.51 (m, 2H), 3.77 (ddd, $J = 4.0$, 7.5, 7.5 Hz, 1H), 3.81 (s, 3H), 4.39 (d, $J = 11.5$ Hz, 1H), 4.44 (d, $J = 11.5$ Hz, 1H), 4.98 (d, $J = 18.0$ Hz, 1H), 5.00 (d, $J = 10.0$ Hz, 1H), 5.77 (ddd, $J = 7.5$, 11.0, 16.5 Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 2H), 7.26 (d, $J = 8.5$ Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ −4.51, −4.37, 14.6, 25.9, 33.3, 43.5, 55.3, 67.1, 72.6, 113.6, 114.6, 129.3, 130.7, 140.7, 159.1; IR (neat) $cm^{-1}$ 3071w, 2953s, 2856m, 1513m, 1520s. Compound **13**: $R_f = 0.65$ (33% EtOAc in hexane); $[\alpha]_D^{23}$ +19.3 [*c* 0.49, $CH_2Cl_2$]; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.06 (d, $J = 7.5$ Hz, 3H), 2.45 (ddd, $J = 3.5$, 4.5, and 16.5 Hz, 1H), 2.50–2.54 (m, 2H), 3.80 (s, 3H), 3.95 (dt, $J = 4.5$ and 6.5 Hz, 1H), 4.45 (d, $J = 11.0$ Hz, 1H), 4.53 (d, $J = 11.0$ Hz, 1H), 5.07 (ddd, $J = 1.5$, 1.5, and 17.0 Hz, 1H), 5.08 (ddd, $J = 1.5$, 1.5, and 10.5 Hz, 1H), 5.77 (ddd, $J = 7.0$, 10.5, and 17.0 Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 2H), 7.24 (d, $J = 9.0$ Hz, 2H), 9.75 (dd, $J = 2.0$ and 3.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 14.2, 40.5, 45.4, 55.5, 71.7, 114.0, 115.9, 129.6, 130.5, 139.9, 159.5, 202.0; IR (neat) $cm^{-1}$ 2967m, 2836m, 1722s, 1512s, 1060s, 918s. Compound **14**: *For the major isomer*: $R_f = 0.65$ [30% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.082 (s, 3H), 0.107 (s, 3H), 0.90 (s, 9H), 0.99 (d, $J = 7.0$ Hz, 3H), 1.19 (s, 9H), 1.20–1.23 (m, 2H), 1.44 (dt, $J = 3.0$, 9.5 Hz, 2H), 1.49–1.61 (m, 4H), 1.74 (dd, $J = 2.0$, 13.0 Hz, 2H), 1.82–1.85 (m, 1H), 2.37–2.46 (m, 2H), 2.58–2.61 (m, 1H), 2.66 (dd, $J = 8.0$, 15.0 Hz, 1H), 3.38–3.42 (m, 1H), 3.75–3.80 (m, 1H), 3.94 (ddd, $J = 4.0$, 4.0, 8.0 Hz, 1H), 4.10 (ddd, $J = 6.0$, 11.0, 11.0 Hz, 1H), 4.13 (ddd, $J = 7.0$, 10.5, 10.5 Hz, 1H), 4.23 (ddd, $J = 4.0$, 8.0, 12.5 Hz, 1H), 5.01 (d, $J = 9.0$ Hz, 1H), 5.02 (d, $J = 18.0$ Hz, 1H), 5.77 (ddd, $J = 7.0$, 10.0, 17.0 Hz, 1H); mass spectrum (APCI): *m/e* (% relative intensity) 535.5 $(M+Na)^+$ (100). Compound **15**: *For the major isomer*: $R_f = 0.20$ [25% EtOAc/hexane]; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.03 (d, $J = 7.0$ Hz, 3H), 1.19 (s, 9H), 1.20–1.32 (m, 2H), 1.48–1.61 (m, 6H), 1.73 (q, $J = 6.5$, 13.0 Hz, 2H), 1.82–1.84 (m, 1H), 2.38 (dd, $J = 5.0$, 15.0 Hz, 2H), 2.54–2.57 (m, 1H), 2.57 (m, 2H), 2.64 (dd, $J = 8.0$, 15.0 Hz, 1H), 3.26 (d, $J = 3.5$ Hz, 1H), 3.39 (dddd, $J = 1.0$, 6.5, 6.5, 12.5 Hz, 1H), 3.69 (dddd, $J = 1.5$, 4.0, 4.0, 8.0 Hz, 1H), 3.75 (m, 1H), 4.11 (ddd, $J = 7.0$, 7.0, 12.5 Hz, 2H), 4.26 (m, 1H), 4.51 (d, $J = 10.5$ Hz, 1H), 4.58 (d, $J = 10.5$ Hz, 1H), 5.05 (ddd, $J = 1.5$, 1.5, 7.5 Hz, 1H), 5.06 (ddd, $J = 1.5$, 1.5, 17.5 Hz, 1H), 5.81 (ddd, $J = 7.5$, 10.5, 17.5 Hz, 1H), 6.87 (d, $J = 9.0$ Hz, 2H), 7.28 (d, $J = 8.5$ Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 18.1, 27.5, 31.3, 31.3, 31.3, 35.2, 35.4, 39.4, 41.5, 42.8, 44.4, 54.1, 55.2, 59.4, 65.0, 68.8, 76.2, 78.4, 78.7, 83.0, 117.9, 117.9, 118.8, 133.6, 133.6, 135.0, 144.8, 163.3, 182.6, 214.4; IR (neat) $cm^{-1}$ 3871m, 3751m, 3677m, 3651m, 3494br s, 2956s, 2936s, 2870s, 2342s, 1719s, 1702s, 1616s; mass spectrum (MALDI): *m/e* (% relative intensity) 541 $(M+Na^+)$ (100), 518 $(M^+)$ (4), 409 (4), 321 (10), 273 (39).


8. (a) Ōmura, K.; Swern, D. *Tetrahedron* **1978**, *24*, 1651; (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
9. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73.
10. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
11. For a review on Sharpless asymmetric epoxidation: Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 247.
12. The enantiomeric excess was determined by chiral HPLC: the retention times of the two enantiomers were 25.789 (*S*) min and 27.861 (*R*) min, respectively. The formation of *R*-(+)-Mosher's ester gave $\geqslant$ 95% de by NMR.
13. Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
14. For the synthesis of key precursor to **12a**, see: (a) Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1787; (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.
15. For the synthesis of key precursor to **12b**, see: Drouet, K. E.; Theodorakis, E. A. *Chem. Eur. J.* **2000**, *6*, 1987.
16. Mukaiyama, T.; Banno, K.; Naraska, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
17. (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619; (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322; (c) Evans, D. A.; Duffy, J. D.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537.
18. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127; (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.