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Total synthesis of (−)-diospongin A and (+)-cryptofolione via asymmetric aldol reaction

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ABSTRACT

Stereoselective synthesis of two distinctive pyranone skeletons diospongin A and cryptofolione has been described based on an asymmetric aldol reaction starting from Chan's diene. The synthetic strategy involves the enantioselective Mukaiyama aldol, diastereoselective reduction of δ-hydroxy-β-keto ester, a tandem sequence of deprotection, and intramolecular oxa-Michael reaction to obtain diospongin A and an asymmetric allylation and lactone formation using ring-closing metathesis reaction to obtain cryptofolione.

Diarylheptanoids are biologically active natural products isolated from Asian herbs or plants.[1] They exhibit various pharmacological activities, such as anti-cancer,[2] anti-inflammatory,[3] and anti-oxidant.[4] Diospongin A and B are isolated from rhizomes of *dioscorea spongiosa* via bioassay-guided fractionation and they possess potent inhibitory activities on bone resorption.[5] Due to significance level of antiosteoporotic activity of diospongins, they have attracted the attention of chemists for the synthesis of these natural products.[6]

6-Substituted 5,6-dihydro α-pyrone, cryptofolione has been isolated from the bark of *Cryptocarya latifolia* and *Cryptocarya myrtifolia*. *Cryptocarya* and *Aniba* species are one of the richest sources of α-pyrones and closely related bicyclic compounds.[7] The styryl α-pyrone skeleton of cryptofolione is closely related to those of goniothalamin, cryptocaryalactone, and strictofoline (Fig. 1).[8a] Most of these α-pyrone derivatives showed cytotoxicity against human tumor cells.[8b,c] Cryptofolione showed activity toward *Trypanosoma cruzi* trypmastigotes, reducing their number by 77% at 250 μg mL^{-1}.[9] *E*/*Z*-Cryptofolione, cryptomoscatone D2 are the inhibitors of the G_2 check point. G_2 check point inhibitors can enhance killing of cancer cells by ionization radiation and DNA-damaging chemotherapeutic agents, particularly in cells lacking p53 function.[10] Therefore, the synthesis of various cryptolactones are of great importance. Till date, only two reports have appeared for the synthesis of cryptofolione.[11]

The earlier synthesis of diospongin A was mostly based on Keck allylation of benzaldehyde[6a–l] and catalytic asymmetric hetero-Diels–Alder reaction.[6j] Over the years much efforts have been directed toward the development of new strategies for the construction of tetrahydropyran rings.[12] Among them enantioselective/asymmetric aldol reaction is the key step in many synthetic strategies.[13] In recent years notable attention has been paid toward the reactivity of acetoacetate ester dianion equivalents **4** and **12**. These dienes have been widely used in the synthesis of enantiopure or racemic δ-hydroxy-β-keto esters **5**, **13,** which are key intermediates in the preparation of many important bioactive compounds.[13f,g] Our synthetic strategy is based on asymmetric aldol, diastereoselective reduction, Wittig reaction, and intramolecular oxa-Michael reaction. This is one of the best alternative approaches for the construction of substituted tetrahydropyran ring in minimum number of steps. In continuation of our research for the synthesis of new bioactive molecules,[14] herein we wish to report a concise synthesis for diospongin A and cryptofolione.

Retrosynthetic plan for diospongin A **1** is outlined in Scheme 1. The key steps involve stereospecific construction of chiral acyclic precursor enone **10,** which could be derived from **5** by a successive implementation of diastereoselective reduction, DIBAL-H reduction, and Wittig reaction. δ-Hydroxy-β-keto ester **5** can be readily prepared from asymmetric Mukaiyama aldol reaction between Chan's diene **4** and benzaldehyde (Scheme 1).

Our synthesis commenced from stereoselective Mukaiyama aldol reaction between Chan's diene[15] **4** and PhCHO **3** using 10 mol % of Ti(O*i*Pr)$_4$/(*S*)-BINOL (1:1). Enantioselective addition of Chan's diene **4** to aldehyde **3** can be performed very efficiently in

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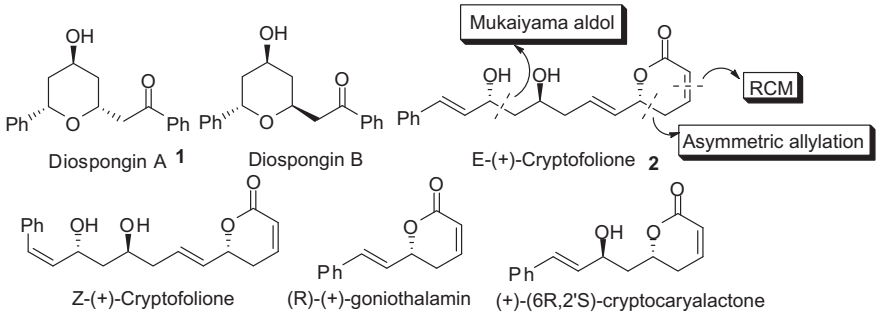
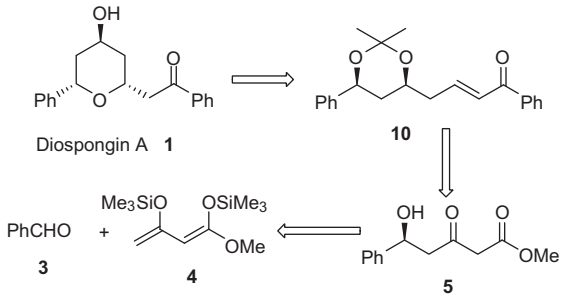


Figure 1. Structures of diospongin A&B and some natural products containing styryl lactones.



Scheme 1. Retrosynthetic strategy of diospongin A **1**.

the presence of catalytic amounts of $Ti(OiPr)_4$/(*S*)-BINOL complex (10 mol %).[16] After purification, the aldol product **5** was obtained in 81% yield with >95% ee as determined by HPLC.[17]

Diastereoselective reduction of the δ-hydroxy-β-keto ester **5** with (2.2 equiv) $Zn(BH_4)_2$[18] at −10 °C afforded the desired *syn*-1,3-diol **6** in 87% yield (*syn:anti* 10:1).[19] In order to prevent unwanted cyclic products, the 1,3-*syn*-diol **6** was protected as acetonide by treating with 2,2-dimethoxy propane and CSA (cat.) to obtain protected diol **7**[20] in 92% yield. Analysis of the unpurified acetonide by ^1H NMR spectroscopy revealed that the *syn* diastereomer was the major product. The stereochemistry of *syn*-1,3 diol was confirmed by the ^{13}C NMR chemical shifts of the acetonide methyl carbon at δ 19.73 and 30.17 and quaternary carbon at δ 99.35, which were characteristic of the acetonide of *syn*-1,3-diols[21] (Fig. 2). Treatment of protected diol **7** with DIBAL-H at 0 °C in THF and the subsequent oxidation using *ortho*-iodoxybenzoic acid (IBX) in CH_2Cl_2/DMSO at 0 °C furnished the corresponding aldehyde **8** in 79% yield (two steps).

The Wittig olefination of aldehyde **8** with phosphorane (**9**) gave enone **10**[22] in 89% yield. Finally, the treatment of enone **10** with CSA (5 mol %) in methanol resulted in tandem deprotection–cycli-

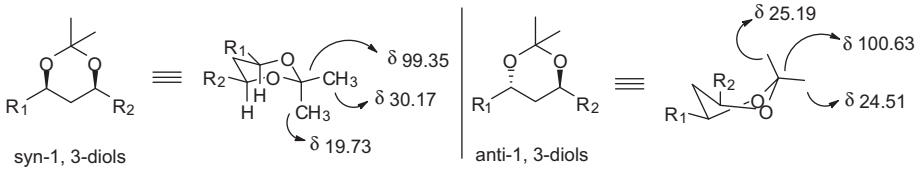
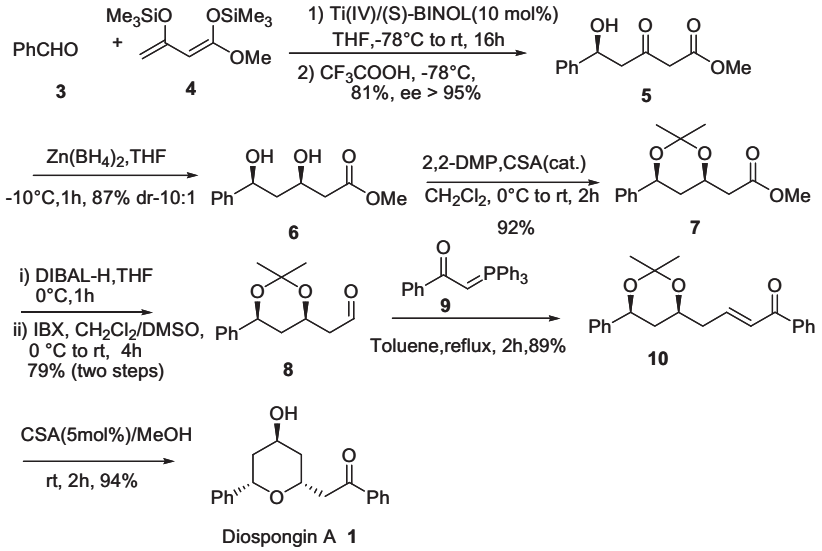


Figure 2. Characteristic conformations and ^{13}C NMR chemical shift values for *syn*- and *anti*-1,3-diols.



Scheme 2. Diospongin A synthesis.

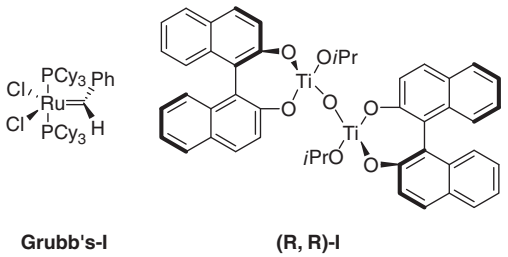


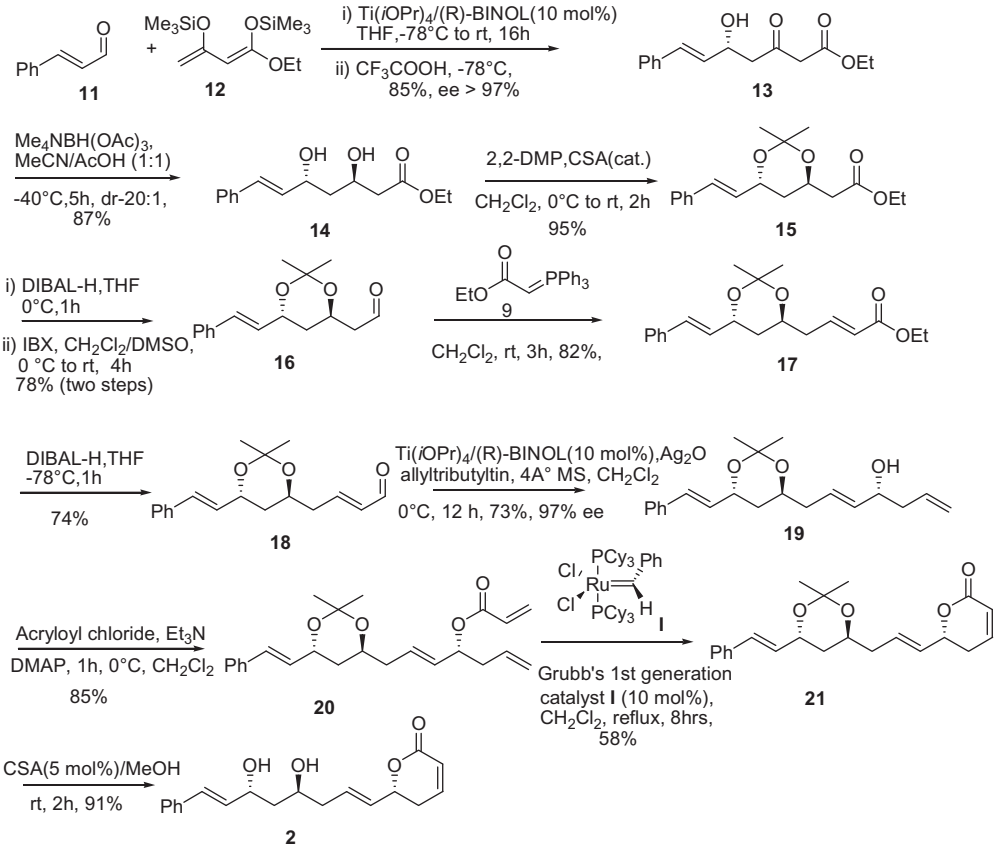
Figure 3. Structures of Grubbs' catalyst **I** and **(R,R)-I**.

zation to yield diospongin A **1**[23] as the only product (Scheme 2). Overall yield in this approach is 38.9%, which was a significant improvement over the earlier methods (overall yield is 29%).[7c] The spectral data and optical rotation {−23.1 (*c* 0.9, $CHCl_3$); lit.: −21.2 (*c* 0.8, $CHCl_3$)} of **1** are in full agreement with that reported for the natural product.[5]

The synthesis of cryptofolione started from steroselective Mukaiyama aldol reaction between Chan's diene[15] **12** and *trans*-cinnamaldehyde **11** using 10 mol % of Ti(O*i*Pr)$_4$/(*R*)-BINOL (1:1) to afford the aldol adduct **13**[16] in 85% with >97% ee as determined by HPLC.[17] *anti*-Selective reduction of **13** with $Me_4NBH(OAc)_3$.[24] in acetonitrile/acetic acid (1:1) at −40 °C resulted in an exclusive formation of *anti*-3,5-dihydroxy ester **14** in 87% yield (*syn*/*anti* 1:20). This 1,3-*anti*-diol **14** was protected as acetonide **15**[25] under conventional reaction conditions using 2,2-dimethoxy propane in CH_2Cl_2 catalyzed by CSA. The stereochemistry of *anti*-1,3 diol was confirmed by ^{13}C NMR chemical shifts of the acetonide methyl groups (Fig. 2). According to Rychnovsky et al.[21a,b] and Evans et al.,[21c] acetonide formed from *syn*-1,3 diols is shown to exist in a well defined chair conformation with two bulky groups on the equatorial position whereas *anti*-1,3-diols adopt a twist boat conformation in order to avoid 1,3-diaxial interaction.

The ester **15** was reduced to alcohol using DIBAL-H in THF at 0 °C, the subsequent oxidation of which by *ortho*-iodoxybenzoic acid (IBX) in CH_2Cl_2/DMSO at 0 °C furnished the corresponding aldehyde **16** (78% two steps). The aldehyde **16** on Wittig homologation with $Ph_3P{=}CHCOOEt$ in refluxing benzene afforded α,β-unsaturated ester **17** favoring the desired *E*-isomer in 82% yield. DIBAL-H reduction of the ester **17** at −78 °C afforded α,β-unsaturated aldehyde **18** in 74% yield, which was subjected to Maruoka allylation[26] in the presence of the titanium complex (**R,R**)-**I** (Fig. 3) and allyltri-*n*-butyltin to furnish the allylic alcohol **19**[27] with the required stereocentre in 73% yield. Acylation of allylic alcohol **19** using acryloyl chloride and Et_3N proceeded smoothly to afford acrylate **20** in 93% yield, which underwent ring-closing metathesis utilizing the first-generation Grubbs' catalyst **I**[28] to furnish cryptofolione acetonide **21**[29] in 58% yield. Finally, the treatment of acetonide **21** with CSA (5 mol %) in methanol afforded cryptofolione **2**[30] (Scheme 3). ^1H and ^{13}C NMR data for cryptofolione completely agree with the natural product data.[7]

In conclusion, we have provided an efficient and stereoselective synthesis of diospongin A and cryptofolione. The key feature of this protocol is the asymmetric Mukaiyama aldol reaction as genesis of chirality and diastereoselective reduction is employed to obtain the desired *syn* and *anti*-1,3-diols. The other steps in this synthetic sequence involve simple and straightforward reactions, such as Wittig reaction, intramolecular Michael reaction to build diastereoselective 2,4,6 *cis* trisubstituted tetrahydropyran ring. Asymmetric allylation and lactone formation using ring-closing metathesis reactions are employed to obtain cryptofolione. The present approach reduces the number of steps and overall yields



Scheme 3. Synthesis of cryptofolione.

of diospongin A and cryptofolione are 38.9% and 10.8%, respectively. The intermediates generated in this protocol may be useful in the total synthesis of related biologically active compounds.

Acknowledgment

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16. *General procedure for the synthesis of* **5:** A mixture of $Ti(OiPr)_4$ (568 mg, 2 mmol), (*S*)-BINOL (572 mg, 2 mmol) and 4 Å molecular sieves (3 g) in THF (20 mL) was stirred at rt for 1 h. Then the mixture was cooled to −78 °C and benzaldehyde **3** (2.12 g, 20 mmol) was added dropwise followed by the addition of silyloxydiene **4** (8.6 ml 40 mmol) over 30 min. The resulting solution was stirred under an inert gas atmosphere at −78 °C for 2 h. It was allowed to attain rt and stirring was continued overnight. The progress of the reaction was monitored by TLC. Upon completion of reaction the mixture was cooled to −78 °C and then TFA (0.4 mL) was added. The solution was warmed to rt and stirring was continued for 1 h. After ensuring the completion of desilylation, the reaction mixture was diluted with ether and neutralized by the dropwise addition of saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was stirred until the evolution of gas ceased (30 min). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to afford a yellow oil. Purification by chromatography on silica gel (30% EtOAc/hexane) afforded the aldol adduct **5** as a pale yellow oil.
Spectral and analytical data of **5**: $[\alpha]_D^{25}$ −56.3 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3418, 2925, 2855, 1736, 1503, 1454, 1420, 1372, 1259, 1162, 1082, 800, 759, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.91 (dd, *J* = 8.9, 3.6 Hz, 2H), 3.45 (s, 2H), 3.73 (s, 3H), 5.16 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.22–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.1, 49.7, 51.6, 69.8, 125.6, 127.8, 128.6, 136.4, 166.9, 202.6; ESI-MS: *m/z* = 245 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{14}H_{16}O_4Na$: 245.0790, found: 245.0793.
Spectral and analytical data of **13**: $[\alpha]_D^{25}$ +13.8 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3450, 3024, 2937, 2861, 1728, 1638, 1576, 1454, 1372, 1259, 1165, 1037, 952, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* = 6.8 Hz, 3H), 2.81 (d, *J* = 6.0, 2H), 3.45 (s, 2H), 4.18 (q, *J* = 7.6 Hz, 2H), 4.74 (m, 1H), 6.15 (dd, *J* = 15.9, 6.0 Hz, 1H), 6.60 (d, *J* = 15.9 Hz, 1H), 7.16–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 49.6, 50.0, 61.6, 68.4, 126.5, 127.8, 128.6, 129.9, 130.6, 136.4, 167.0, 202.7; ESI-MS: *m/z* = 285 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{14}H_{16}O_4Na$: 285.1103, found: 285.1109.
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20. *Spectral and analytical data of* **7**: $[\alpha]_D^{25}$ −52.5 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3081, 2922, 2853, 1740, 1640, 1539, 1459, 1378, 1259, 1201, 1164, 965, 799, 701, 536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (dt, *J* = 13.5, 2.9 Hz, 1H), 1.40 (s, 3H), 1.50 (s, 3H), 1.74 (dt, *J* = 13.5, 2.9 Hz, 1H), 2.31 (dd, *J* = 15.4, 5.8 Hz, 1H), 2.50 (dd, *J* = 15.4, 6.7 Hz, 1H), 3.60 (s, 3H) 4.33–4.41 (m, 1H), 4.84 (dd, *J* = 11.5, 1.9 Hz, 1H), 7.13–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.73, 30.17, 38.84, 41.14, 51.70, 66.12, 71.33, 99.35, 125.91, 127.69, 128.47, 142.05, 171.35; ESI-MS: *m/z* = 287 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{15}H_{20}NaO_4$: 287.1259, found: 287.1260.
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22. *Spectral and analytical data of* **10**: $[\alpha]_D^{25}$ −41.3 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3011, 2921, 2852, 1733, 1641, 1581, 1459, 1377, 1201, 1137, 1024, 760, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (dt, *J* = 12.8, 7.5 Hz, 1H), 1.43 (s, 3H), 1.50 (s, 3H), 1.72–1.71 (dt, *J* = 12.8, 2.7 Hz, 1H), 2.38 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.50 (dd, *J* = 14.4, 6.8 Hz, 1H), 4.11 (m, 1H), 4.82 (dd, *J* = 11.3, 2.3 Hz, 1H), 6.90 (d, *J* = 15.9 Hz, 1H), 7.01 (dt, *J* = 15.9, 8.10 Hz, 1H), 7.13–7.31 (m, 5H), 7.39 (t, *J* = 7.5 Hz, 2H) 7.47 (t, *J* = 6.79 Hz, 1H), 7.85 (d, *J* = 8.10 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.69, 29.16, 38.14, 38.61, 67.07, 70.20, 95.05, 124.70, 126.45, 126.84, 127.24, 127.35, 127.47, 131.49, 136.71, 141.01, 143.25, 188.63; ESI-MS: *m/z* = 359 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{22}H_{24}NaO_3$: 359.1623, found: 359.1639.
23. *Spectral and analytical data of* **1**: mp 102–105 °C. $[\alpha]_D^{25}$ −23.1 (*c* 0.9, $CHCl_3$); IR (neat): ν_{max} 3375, 2923, 2855, 1688, 1590, 1450, 1258, 1060, 919, 750, 694, 534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58–1.79 (m, 2H), 1.91–1.98 (m, 2H), 3.07 (dd, *J* = 15.86, 6.80 Hz, 1H), 3.41 (dd, *J* = 15.86, 6.01 Hz, 1H), 4.38 (t, *J* = 3.02 Hz, 1H) 4.65 (m, 1H), 4.94 (dd, *J* = 11.33, 1,51 Hz, 1H), 7.19–7.37 (m, 5H), 7.52 (t, *J* = 7.55 Hz, 2H) 7.68 (t, *J* = 6.04 Hz, 1H) 7.91 (d, *J* = 6.80 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.67, 40.29, 45.17, 64.66, 69.06, 73.85, 125.82, 127.20, 128.22, 128.44, 128.53, 133.03, 142.78, 197.89; ESI-MS: *m/z* = 319 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{19}H_{20}NaO_3$: 319.1310, found: 319.1315.
24. (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560; (b) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.
25. *Spectral and analytical data of* **15**: $[\alpha]_D^{25}$ −19.6 (*c* 0.6, $CHCl_3$); IR (neat): ν_{max} 3220, 2983, 2863, 1738, 1638, 1592, 1510, 1468, 1378, 1327, 1232, 1021, 984, 769, 634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* = 6.8 Hz, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.77 (ddd, *J* = 9.8, 6.8, 6.1 Hz, 1H), 1.92 (ddd, *J* = 9.8, 6.8, 6.1 Hz, 1H), 2.41 (dd, *J* = 15.1, 6.1 Hz, 1H), 2.53 (dd, *J* = 15.1, 7.6 Hz, 1H), 4.14 (q, *J* = 7.5 Hz, 2H) 4.32 (m, 1H), 4.48 (m, 1H), 6.17 (dd, *J* = 15.9, 6.0 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 7.15–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 24.5, 25.2, 37.2, 40.8, 60.4, 63.2, 67.5, 100.6, 126.4, 127.6, 128.4, 129.4, 130.5, 136.5, 170.8; ESI-MS: *m/z* = 327 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{18}H_{24}NaO_4$: 327.1572, found: 327.1587.
26. (a) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708; (b) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem. Eur. J.* **2003**, *9*, 4405.
27. *Spectral and analytical data of* **19**: $[\alpha]_D^{25}$ +40.8 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3440, 2927, 2873, 1678, 1621, 1549, 1459, 1373, 1288, 1172, 1024, 790, 658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.4 (s, 3H), 1.69–1.87 (m, 2H), 2.20–2.36 (m, 4H), 3.91 (m, 1H), 4.11 (dt, *J* = 6.2, 5.8 Hz, 1H), 4.47 (dt, *J* = 7.9, 5.8 Hz, 1H), 5.10 (m, 1H), 5.13 (dd, *J* = 5.48, 2.0 Hz, 1H), 5.56 (dd, *J* = 15.5, 5.7 Hz, 1H), 5.65 (dt, *J* = 15.5, 6.2 Hz, 1H), 5.72–5.86 (m, 1H), 6.17 (dd, *J* = 16.2, 6.0 Hz, 1H), 6.51 (d, *J* = 16.2 Hz, 1H), 7.09–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 25.3, 37.4, 38.5, 41.2, 65.0, 67.4, 78.4, 100.7, 114.3, 126.4, 127.7, 128.5, 129.2, 130.6, 130.9, 131.5, 134.6, 136.4; ESI-MS: *m/z* = 351 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{21}H_{28}NaO_3$: 351.1936, found: 351.1945.
28. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.
29. *Spectral and analytical data of* **21**: $[\alpha]_D^{25}$ +62.3 (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3044, 2973, 2896, 1727, 1646, 1630, 1581, 1534, 1450, 1431, 1365, 1321, 1160, 1124, 972, 572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.40 (s, 3H), 1.68–

1.90 (m, 2H), 2.19–2.34 (m, 2H), 2.35–2.45 (m, 2H), 3.92 (m, 1H), 4.48 (m, 1H), 4.90 (m, 1H), 5.70 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.85 (dt, *J* = 15.5, 7.6 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 6.24 (dd, *J* = 16.2, 6.2 Hz, 1H), 6.58 (d, *J* = 16.2 Hz, 1H), 6.87 (dt, *J* = 9.8, 4.6 Hz, 1H), 7.14–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 25.4, 30.0, 37.5, 38.6, 65.5, 67.6, 78.2, 100.6, 126.5, 127.7, 128.5, 129.6, 130.5, 130.9, 131.5, 134.6, 136.5, 144.6, 164.2; ESI-MS: *m/z* = 377 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{22}H_{26}NaO_4$: 377.1729, found: 377.1737.

30. *Spectral and analytical data of* **2**: $[\alpha]_D^{25}$ **+**56.5 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3630, 3083, 2935, 2851, 1738, 1703, 1658, 1622, 1589, 1504, 1453, 1374, 1241, 1120, 962, 724 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68–1.90 (m, 2H), 2.24 (t, *J* = 6.5 Hz, 2H), 2.41 (t, *J* = 6.2 Hz, 2H), 3.61 (br, 2H), 4.06 (m, 1H), 4.64 (m, 1H), 4.86 (m, 1H), 5.65 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.86 (dt, *J* = 15.5, 7.6 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 6.25 (dd, *J* = 16.2, 6.2 Hz, 1H), 6.62 (d, *J* = 16.2 Hz, 1H), 6.85 (dt, *J* = 9.8, 4.6 Hz, 1H), 7.14–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 40.5, 42.4, 68.4, 70.4, 78.2, 126.5, 127.6, 128.5, 129.8, 130.5, 131.0, 131.5, 136.6, 144.8, 164.2; ESI-MS: *m/z* = 337 (M^++Na); ESI-HRMS: *m/z* calcd for $C_{19}H_{22}NaO_4$: 337.1416, found: 337.1422.