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Total synthesis of the novel *seco*-prezizaane sesquiterpenoid (+)-1*S*-minwanenone

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Abstract—The first total synthesis of (+)-1*S*-minwanenone, an archetypical *seco*-prezizaane sesquiterpene, has been accomplished from a readily available chiral *endo*-tricyclic synthon following a flexible strategy.

seco-Prezizaane-type sesquiterpenes belong to a biogenetically intriguing and structurally unique class of natural products, which occur extensively in the exotic *Illicium* species.[1] In structural terms, *seco*-prezizaanes embody a compact, cage-like architecture, embellished with dense and diverse oxygen functionalities with attendant stereochemical variations, within their complex framework as depicted through the archetypical examples **1**–**4** (Fig. 1).

Given such notable structural attributes, *seco*-prezizaanes present themselves as novel scaffolds for exploring their therapeutical potential. Indeed, several members of this family exhibit bioactivity profiles ranging from neurotoxicity to promoters of neurite growth on one hand and as promising inhibitors of GABA action in the central nervous system on the other.[2] Consequently, total synthesis endeavours towards this class of natural products is an arena of contemporary interest and challenge; however, only limited attention has been bestowed in this quest.[3] It was felt that synthetic endeavours of general utility towards *seco*-prezizaane could also be strategically diverted and varied to provide access to newer, cage-like polycyclic scaffolds with different functionality.

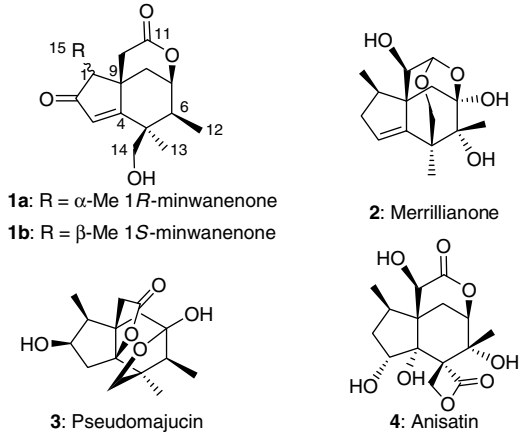

Figure 1. Representative examples of *seco*-prezizaane type natural products.

In our laboratory, efforts are currently directed towards developing a general protocol to access several members of the *seco*-prezizaanes class of natural products from a common intermediate. As the initial installment of such endeavours, we describe the first total synthesis of (+)-1*S*-minwanenone **5**, an enantiomer of the natural product (−)-1*R*-minwanenone **1a** and a prototypical member of the *seco*-prezizaane family.[1] During our successful journey towards (+)-1*S*-minwanenone **5**, we witnessed the formation of the tetracyclic core present in the natural product merrillianone **2**, which in turn underscores the intrinsic adaptability of our synthetic approach towards the other members of this complex family.[4]

During their extensive searches for biologically active substances from the *Illicium* species, Fukuyama and co-workers reported the isolation of (−)-1*R*-minwanenone **1a** and its epimer (−)-1*S*-minwanenone **1b** along with several other *seco*-prezizaane type sesquiterpenoids from the methanol extract of the pericarps of *Illicium*

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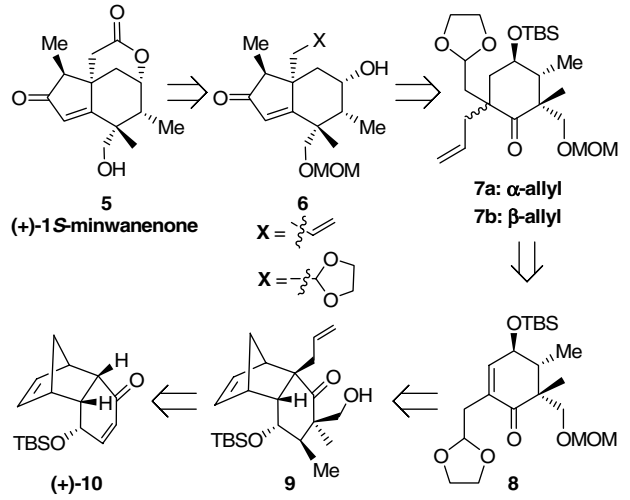
minwanense.[1] The structures of minwanenones **1a** and **1b** were established through extensive NMR studies and the evident kinship with other co-occurring natural products was harnessed to deduce their absolute configuration.[1] From a synthetic point of view, the tricyclic skeleton of minwanenones **1a**,**b** comprising five stereocentres, amongst which two are quaternary, and with functional groups such as a bridged lactone, enone and a primary hydroxyl group accounting for four oxygens, poses considerable challenges. Evolution of our synthetic strategy towards this target also factored in potential generalization towards other members of this family.

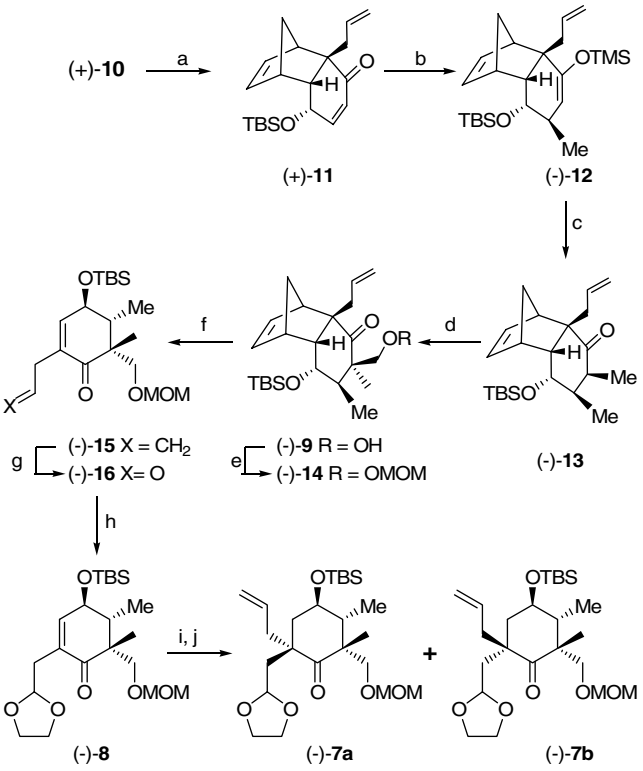
Retrosynthetically, it was envisaged that (+)-1*S*-minwanenone **5** could be derived from an appropriately functionalized bicyclic enone **6**, which in turn could be obtained via intramolecular aldol condensation in a 1,4-diketone precursor, suitably crafted from either of the diastereomeric allylated cyclohexanones **7a**,**b**. Indeed, the allyl group in **7a**,**b** is strategically placed to function either as a 'masked acetaldehyde' or as an 'acetone equivalent' to render both the anticipated diastereomers serviceable towards the target structure. Access to **7a**,**b** could be devised from cyclohexenone **8** by orchestrating appropriate FGIs and allylation. Cyclohexenone **8** was to be obtained from (+)-**10** via the intermediacy of **9** (Scheme 1). The choice of the *endo*-tricyclic chiral synthon (+)-**10** (available in both enantiomeric forms),[5] as the starting platform, was a key tactic as its well established propensity towards reactivity on the *exo*-face due to inherent topological bias was to enable the stereoselective installation of the C5, C6 stereogenic centres in the early stages of the synthesis.

Allylation of the readily available chiral synthon (+)-**10** was smooth and stereoselectively furnished *exo*-(+)-**11**. Copper(I) mediated 1,4-addition[6] of MeMgI to (+)-**11** proceeded with excellent *exo*-face selectivity and in situ enolate capture delivered (−)-**12** as a single diastereomer. Quenching the lithium enolate generated from enol–TMS ether (−)-**12** with MeI provided the dimethylated product (−)-**13**. The C5 quaternary centre, with requisite relative disposition with respect to C6, was now set through stereoselective α-hydroxymethylation of (−)-**13** from the *exo*-face to deliver alcohol (−)-**9** (Scheme 2). The free hydroxyl group in (−)-**9** was protected as MOM derivative (−)-**14** prior to removal of the norbornyl scaffold. Thermal activation in (−)-**14** disengaged the norbornyl moiety through a facile retro Diels–Alder process to provide cyclohexenone (−)-**15**. A single pot OsO_4–$NaIO_4$ mediated oxidative cleavage[7] of the allyl group in (−)-**15** furnished aldehyde (−)-**16**, which was protected as acetal (−)-**8** (Scheme 2). Sequential catalytic hydrogenation and allylation of (−)-**8** afforded the diastereomers (−)-**7a** and (−)-**7b** in a 60:40 ratio (Scheme 2). The anticipated stereochemical divergence leading to the formation of both (−)-**7a** and (−)-**7b** could be fashioned into stereochemical convergence that rendered both the diastereomers serviceable (vide infra).

Our first foray towards the natural product **1** was quite understandably through the major diastereomeric product (−)-**7a**. Selective deprotection of the acetal moiety in (−)-**7a** provided the free aldehyde (−)-**17**. Chemo- and regioselective addition of MeLi to aldehyde (−)-**17**, followed by PCC oxidation furnished diketone (−)-**18**. Exposure of (−)-**18** to NaH in THF effected the intramolecular aldol condensation to deliver bicyclic enone



Scheme 1. Retrosynthetic analysis.

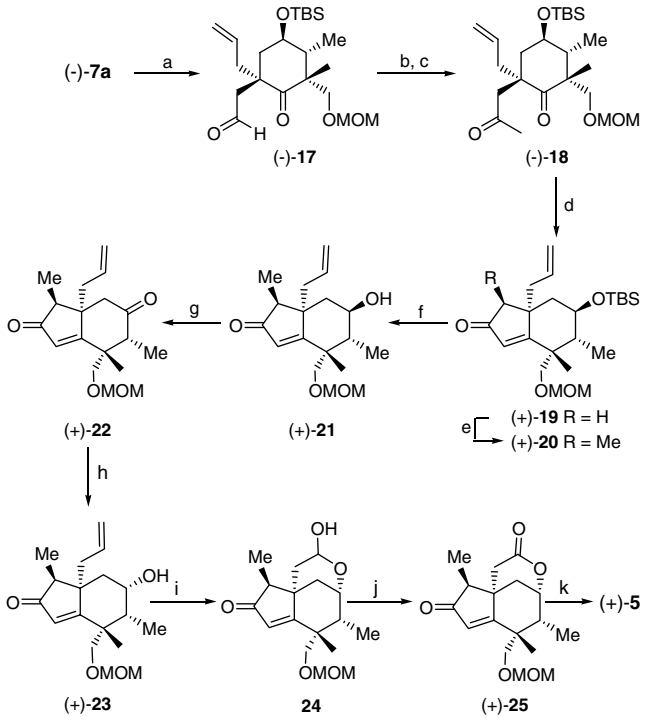


Scheme 2. Reagents and conditions: (a) LHMDS, THF, allyl bromide, −20 °C, 93%; (b) MeMgI, CuBr·DMS, THF, TMSCl, −78 °C, 92%; (c) *n*-BuLi, HMPA, THF, MeI, 0 °C, 1.5 h, 85%; (d) DBU, THF, formalin, 12 h, 90% (borsm/based on recovered starting material); (e) DIPEA, DMAP(cat.), MOMCl, DCM, 6 h, 93%; (f) Ph_2O, 210 °C, 15 min, 95%; (g) OsO_4 (cat.), $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1), 0 °C, 1 h, 65%; (h) ethylene glycol, PPTS, benzene, Dean–Stark, 80 °C, 2 h, 88%; (i) PtO_2, H_2 (1 atm), rt, 1 h, 95%; (j) NaH, allyl bromide, THF, 65 °C, 2 h, 96%.

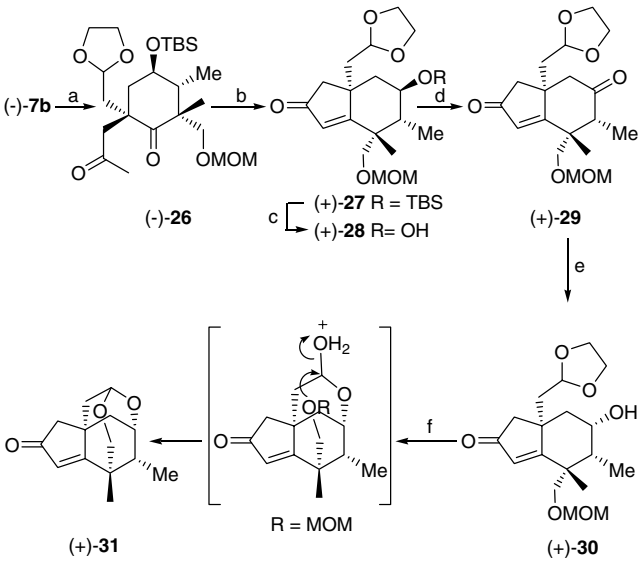
(+)-**19**. Methylation of (+)-**19** under kinetically controlled conditions was stereoselective and afforded (+)-**20** as a single isomer. Deprotection of TBS in (+)-**20** proceeded smoothly to furnish alcohol (+)-**21**, which on subsequent oxidation provided ketone (+)-**22**. Regio- and stereoselective reduction of (+)-**22** furnished (+)-**23** having the desired C7 hydroxyl stereochemistry. Oxidative cleavage[7] of the allyl group in (+)-**23** was achieved by following an improved procedure for one-pot OsO_4–$NaIO_4$ oxidation to furnish a mixture of lactols **24**. Fetizon oxidation[8] of lactols **24** provided the tricyclic lactone (+)-**25**. Finally, the MOM group in (+)-**25** was removed employing triphenylcarbenium-tetrafluoroborate[9] to provide (+)-1*S*-minwanenone (+)-**5**, which was found to be spectroscopically (^1H and ^{13}C NMR spectra) identical with the natural product (−)-1*R*-minwanenone **1** (Scheme 3).[1,10] However, its specific rotation + 23.3 (*c* 0.3, EtOH) was opposite to that reported for the natural (−)-1*R*-minwanenone **1**.[1] Our total synthesis of *ent*-natural product (+)-**5** from the chiral synthon (+)-**10** of well established absolute stereochemistry also secures the previously assigned absolute configuration of the natural product.[1]

Having accomplished the total synthesis of (+)-**5** from the stereochemically defined cyclohexanone (−)-**7a**, it was of interest to demonstrate the serviceability of its diastereomeric sibling (−)-**7b** to showcase the concept of stereochemical convergence. Wacker oxidation[11] of (−)-**7b** delivered diketone (−)-**26**, the projected precursor for intramolecular aldol condensation. Exposure of (−)-**26** to NaH in THF resulted in the generation of functionally embellished bicyclic enone (+)-**27** (Scheme 4). Deprotection of TBS in (+)-**27** to (+)-**28** and PCC oxidation led to dione (+)-**29**. Chemo- and stereoselective reduction of (+)-**29** provided (+)-**30** with the desired stereochemical orientation at the C7-hydroxyl bearing stereocentre. At this stage, deprotection of the acetal moiety in (+)-**30** was to reveal the aldehyde group to concomitantly engage the C7-hydroxyl to form a lactol, which on further oxidation was expected to deliver the tricyclic skeleton of minwanenone. However, attempts to deprotect the acetal group in (+)-**30** under acidic conditions resulted in the generation of a tetracyclic framework (+)-**31**, representing a conspicuous motif present in cycloparvifloralone type[4b] natural products, for example, merrillianone **2**,[4a] through intramolecular acetalization involving the deprotected aldehyde and the distal but stereochemically well poised hydroxyl groups. Facile formation of (+)-**31** reveals the interactive proclivities of functionalities on this framework and augurs well for the applicability of this route to access other *seco*-prezizaane natural products.[4]

In summary, the first total synthesis of (+)-1*S*-minwanenone, a prototypical *seco*-prezizaane, has been accomplished from a readily available chiral building block with 2.5% overall yield. The approach outlined here exploits the interplay of stereochemical divergence and subsequent convergence to assemble the functionally embellished bicyclo[4.3.0]nonane core present in *seco*-prezizaanes. Adaptation of this protocol towards the synthesis of other *seco*-prezizaane natural products is currently in progress.



Scheme 3. Reagents and conditions: (a) Amberlyst-15, acetone, rt, 3 h, 65%; (b) MeLi, THF, −78 °C, 30 min; (c) PCC, NaOAc, silica, DCM (85% for two steps); (d) NaH, THF, rt, 5 h, then 65 °C, 2 h, 85%; (e) LHMDS, THF, HMPA, −40 to 0 °C, 1.5 h, then MeI, −40 to 0 °C, 2 h, 74%; (f) TBAF, THF, rt, 8 h, 92%; (g) PCC, NaOAc, silica, DCM, 3 h, 90%; (h) $NaBH_4$, THF/MeOH (1:1), −78 °C, 2 min, 95%; (i) OsO_4(cat.), $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1), 0 °C, 1.5 h, 80%; (j) Ag_2CO_3 on Celite, benzene, 80 °C, 6 h, 90%; (k) triphenylcarbenium tetrafluoroborate, DCM, 0–10 °C, 1 h, 70% (borsm).



Scheme 4. Reagents and conditions: (a) $PdCl_2$, CuCl, O_2, rt, 8 h, 77%; (b) NaH, THF, rt, 5 h, then 65 °C, 2 h, 80%; (c) TBAF, THF, rt, 10 h, 91%; (d) PCC, NaOAc, silica, DCM, rt, 3 h, 90%; (e) $NaBH_4$, THF/MeOH (1:1), −78 °C, 2 min, 95%; (f) PPTS, acetone, reflux, 8 h, 92% or Amberlyst-15, acetone, rt, 6 h, 90%.

Acknowledgements

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References and notes

1. Yokoyama, R.; Huang, J.-M.; Hosoda, A.; Kino, K.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2003**, *66*, 799–803.
2. (a) Niwa, H.; Yamada, K. *Farumashia* **1991**, *27*, 924–927; (b) Fukuyama, Y.; Shida, N.; Kodama, M. *Planta Med.* **1993**, *59*, 181–182; (c) Fukuyama, Y.; Shida, N.; Kodama, M.; Chaki, H.; Yugami, T. *Chem. Pharm. Bull.* **1995**, *43*, 2270–2272; (d) Huang, J.-M.; Yokoyama, R.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2001**, *64*, 428–431; (e) Yokoyama, R.; Huang, J.-M.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65*, 527–531; (f) Schmidt, T. J.; Gurrath, M.; Ozoe, Y. *Bioorg. Med. Chem.* **2004**, *12*, 4159–4167.
3. (a) Wilson, R. M.; Danishefsky, S. J. *Acc. Chem. Res.* **2006**, *39*, 539–549; (b) Cho, Y. S.; Carache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358–14359; (c) Niwa, H.; Nisiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Mori, T.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001–9003; (d) Kende, A. S.; Chen, J. *J. Am. Chem. Soc.* **1985**, *107*, 7184–7186.
4. (a) Huang, J.-M.; Yang, C.-S.; Wang, H.; Wu, Q.-M.; Fukuyama, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1749–1752; (b) Schmidt, T. J. *J. Nat. Prod.* **1999**, *62*, 684–687.
5. (a) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogaswara, K. *Synthesis* **1993**, 948–950; (b) Hiroya, K.; Uwai, K.; Ogasawara, K. *Chem. Pharm. Bull.* **1995**, *43*, 901–903; (c) Nakashima, H.; Hiroya, K.; Taniguchi, T.; Ogasawara, K. *Synlett* **1999**, 1405–1406; (d) Konno, H.; Ogaswara, K. *Synthesis* **1999**, 1135–1140; (e) Mehta, G.; Islam, K. *Synlett* **2000**, 1473–1475; (f) Mehta, G.; Shinde, H. M. *Chem. Commun.* **2005**, 3703–3705.
6. Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025–4028.
7. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.
8. Fetizon, M.; Golfier, M.; Mourgues, P. *Tetrahedron Lett.* **1972**, *13*, 4445–4448.
9. (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935; (b) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542–552.
10. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Spectral data of selected compounds. Compound (−)-**7a**. $[\alpha]_D^{27}$ −55.0 (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2929, 1695, 1471 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76–5.63 (m, 1H), 5.14–5.08 (m, 2H), 4.80 (t, $J = 5.1$ Hz, 1H), 4.50 (ABq, $J = 6.6$ Hz, 2H), 4.12 (dt, $J = 9.9$ and 3.9 Hz, 1H), 3.99–3.80 (m, 1H), 3.82–3.67 (m, 3H), 3.47 (s, 2H), 3.31 (s, 3H), 2.46 (dd, $J = 14.1$ and 7.8 Hz, 1H), 2.29–2.18 (m, 2H), 2.04–1.81 (m, 3H), 1.69 (dd, $J = 14.1$ and 4.8 Hz, 1H), 1.06 (d, $J = 6.6$ Hz, 3H), 1.06 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.51, 133.78, 118.73, 102.41, 96.71, 74.20, 68.68, 64.84, 63.99, 55.65, 51.93, 49.25, 47.05, 41.86, 40.91, 40.37, 25.92, 22.83, 18.08, 12.27, −4.05, −4.59; HRMS(ES) *m/z* calcd for $C_{24}H_{44}SiO_6$ ($M+Na^+$) 479.2805, found: 479.2813. Compound (−)-**7b**. $[\alpha]_D^{22}$ −25.0 (*c* 1.0, $CHCl_3$); IR (neat) 3077, 2930, 2857, 1695, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.55 (m, 1H), 5.11–5.01 (m, 2H), 4.80 (dd, $J = 5.1$ and 3.9 Hz, 1H), 4.53 (d(1/2ABq), $J = 6.9$ Hz, 1H), 4.47 (d(1/2ABq), $J = 6.9$ Hz, 1H), 4.13 (dt, $J = 9.9$ and 4.2 Hz, 1H), 3.97–3.70 (m, 4H), 3.48 (ABq, $J = 9.1$ Hz, 2H), 3.32 (s, 3H), 2.59 (dd, $J = 13.5$ and 6.6 Hz, 1H), 2.24 (dd, $J = 13.5$ and 5.4 Hz, 1H), 2.07–1.66 (m, 5 H), 1.05 (d, $J = 6.9$ Hz, 3H), 1.02 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.91, 134.15, 118.82, 102.27, 96.74, 73.76, 69.10, 64.65, 64.23, 55.58, 51.88, 49.81, 47.08, 43.01, 41.57, 40.58, 25.91, 22.35, 18.08, 12.53, −4.18, −4.72; HRMS(ES) *m/z* calcd for $C_{24}H_{44}SiO_6$ ($M+Na^+$) 479.2805, found: 479.2805. Compound (+)-**19**. $[\alpha]_D^{24}$ +48.0 (*c* 1.0, $CHCl_3$); IR (neat) 3077, 2930, 1698, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.77–5.63 (m, 1H), 5.13–5.07 (m, 2H), 4.56 (s, 2H), 3.85–3.75 (m, 2H), 3.49 (d(1/2ABq), $J = 9.6$ Hz, 1H), 3.34 (s, 3H), 2.51 (d(1/2ABq), $J = 18.0$ Hz, 1H), 2.42 (d, $J = 6.9$ Hz, 2H), 2.24 (dd, $J = 13.2$ and 4.2 Hz, 1H), 2.10 (d(1/2ABq), $J = 18.0$ Hz, 1H), 1.49–1.37 (m, 2H), 1.35 (s, 3H), 1.06 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.18, 187.49, 133.90, 131.56, 119.18, 97.02, 71.21, 68.87, 55.70, 50.81, 49.22, 47.41, 46.78, 43.95, 42.50, 25.76, 24.56, 17.95, 12.04, −4.05, −4.67; HRMS(ES) *m/z* calcd for $C_{23}H_{40}SiO_4$ ($M+Na^+$) 431.2594, found 431.2596. Compound (+)-**5**. $[\alpha]_D^{22}$ +23.3 (*c* 0.3, EtOH); IR (neat) 3424, 2930, 1729, 1703, 1603 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 6.04 (s, 1H), 4.68 (m, 1H), 3.63 (d, $J = 11.5$ Hz, 1H), 3.49 (d, $J = 11.5$ Hz, 1H), 2.89 (d, $J = 19.0$ Hz, 1H), 2.81 (dd, $J = 19.0$ and 2.0 Hz, 1H), 2.32 (dd, $J = 13.5$ and 4.0 Hz, 1H), 2.18 (q, $J = 7.5$ Hz, 1H), 1.85 (dq, $J = 7.5$ and 3.0 Hz, 1H), 1.80 (ddd, $J = 14.0$, 2.0 and 2.0 Hz, 1H), 1.36 (s, 3H), 1.19 (d, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 8.0$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 211.11, 188.20, 173.48, 130.85, 81.32, 65.42, 53.03, 46.78, 46.25, 45.43, 41.71, 35.13, 24.85, 12.15, 10.05; HRMS(ES) *m/z* calcd for $C_{15}H_{20}O_4$ ($M+Na^+$) 287.1259, found 287.1260. Compound (+)-**31**. Mp 131–131.5 °C; $[\alpha]_D^{27}$ +122.5 (*c* 0.6, $CHCl_3$); IR (neat) 2939, 1701, 1682, 1599 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.34 (d, $J = 5.1$ Hz, 1H), 3.96–3.94 (m, 1H), 3.84 (d(1/2ABq), $J = 12.3$ Hz, 1H), 3.54 (d(1/2ABq), $J = 12.0$ Hz, 1H), 2.29–2.18 (m, 4H), 1.83–1.78 (m, 2H), 1.65–1.62 (m, 1H), 1.34 (d, $J = 7.2$ Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.23, 191.49, 123.65, 94.82, 72.62, 71.51, 49.61, 46.32, 44.96, 41.47, 40.17, 37.45, 21.02, 12.60; HRMS(ES) *m/z* calcd for $C_{14}H_{18}O_3$ ($M+Na^+$) 257.1154, found 257.1156.
11. Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *17*, 2975–2976.