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Model synthetic studies toward jiadifenin and majucin type *seco*-prezizaane natural products via a stereo- and enantioselective approach

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ABSTRACT

A concise stereo- and enantioselective approach to *seco*-prezizaane sesquiterpenoids, leading to the acquisition of two bicyclic fragments, is delineated.

seco-Prezizaane sesquiterpenoids have emerged as a growing and diverse family of sesquiterpenoids, embodying complex polycyclic architecture with varied oxygen functionalities.[1] Interestingly, the *seco*-prezizaane natural products have been encountered only among the exotic and widely distributed *Illicium* species and this resource has been extensively explored in recent years by the group of Fukuyama among others.[1]

In Figure 1 are displayed several representative types among the *seco*-prezizaane natural products. Among them, those belonging to the jiadifenin core **1**–**2** and their biogenetic siblings of majucin-prototype **3**–**7** hold instant appeal in view of their compact, highly oxy-functionalized, cage-like molecular architecture and the very special kind of bioactivity profile displayed by them.

Indeed, jiadifenin **1**,[1e] jiadifenolide A **2**[1h], and majucin derivatives **3**[1h] and **5**[1e] have been shown to exhibit neurotrophic activity by promoting neurite outgrowth in primary cultures of rat cortical neurons at 0.1–10 μM concentration. It has also been observed that natural product jiadifenin **1** up-regulates the neurite outgrowth activity of nerve growth factor (NGF), a natural neurotrophin.[1,2b] These impressive bioactivity attributes, which have implications in maintaining neuronal health and in addressing neurodegeneration related disorders like Alzheimer's, make *seco*-prezizaanes natural products unique for exploring the chemical diversity space around their scaffold and for mapping their therapeutic potential.[2a–c]

First total synthesis of jiadifenin **1** was accomplished by the group of Danishefsky[2a,b] and more recently Theodorakis et al.[2c,e] have reported a synthesis of jiadifenin **1** as well as of related jiadifenolide **2**. A model study toward the tricyclic core of **1** has also appeared recently.[2d] Our group has been interested in the synthesis of neurotrophically active natural products in general[3] and of *seco*-prezizaanes natural products in particular and we have recently accomplished the total synthesis of merrilactone A[3a,b] and of α-minwanenone **8**.[3c] As part of our continuing synthetic efforts in the area, we have been drawn to jiadifenin and majucin type natural products. Herein, we report a stereo- and enantioselective approach toward the core bicyclic fragments present in them, representing functionalized AB and BC rings. A very recent observation[1i] that even a simpler, truncated derivative like **7** of jiadifenin-majucin type *seco*-prezizaane promoted impressive neurite outgrowth at low μM concentrations, lends relevance to our endeavors disclosed in this Letter.

A retrosynthetic perspective on an approach to jiadifenin-majucin frameworks (**1** and **9**) and leading to the functionalized fragments **10** (AB rings) and **11** (BC rings) is displayed in Scheme 1. A basic premise of this fragment based model conception was that once the core strategies leading to the two segments **10** and **11** were successfully executed, they could be unified to target the natural products of this family. Our approach to both the fragments **10** and **11** emanated from a common chiral synthon (+)-**12**, readily accessible from commercially available cyclopentadiene and *p*-benzoquinone as per the protocols described earlier.[4] A key feature of our approach was the elaboration of the six-membered ring of

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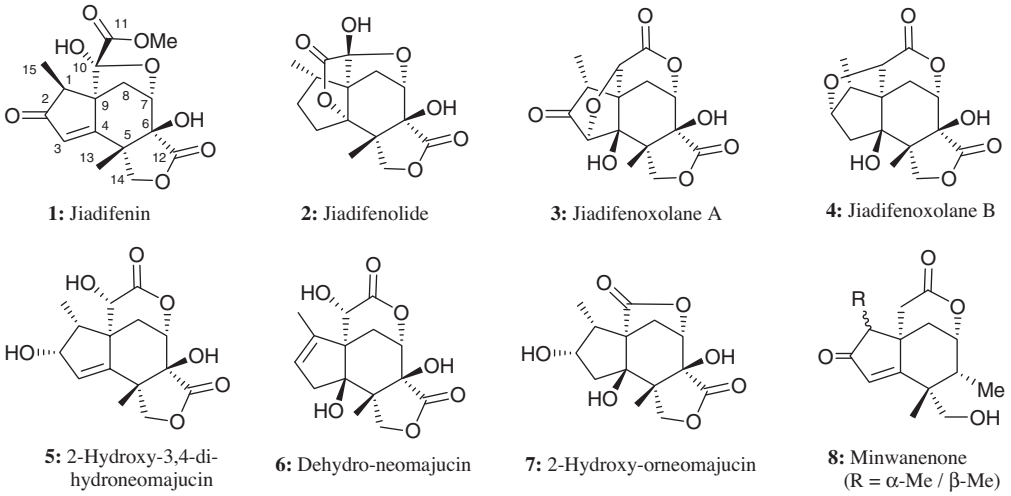


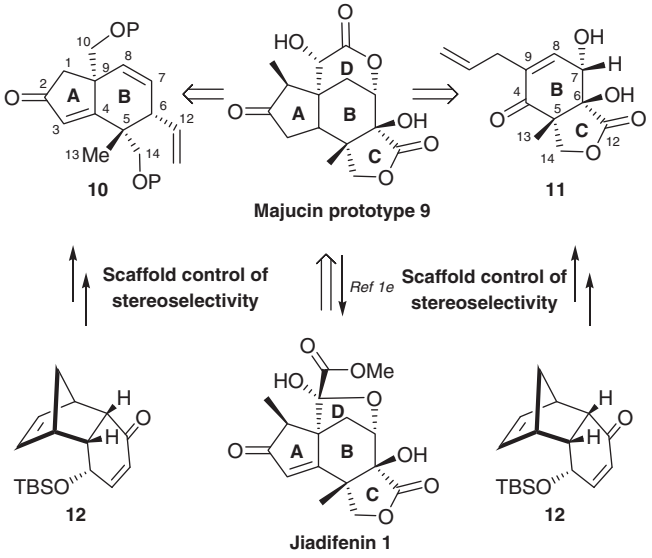
Figure 1. Representative types among *seco*-prezizaane sesquiterpenoids.

synthon (+)-**12** into a stereochemically embellished ring 'B' of the target natural products by harnessing the *exo*-face (convex face) selectivity inherent to its tricyclic framework. In particular, the intent was to secure the stereochemistry at the quaternary centers at C4, C5, and C9 and concurrently install the requisite functionality.

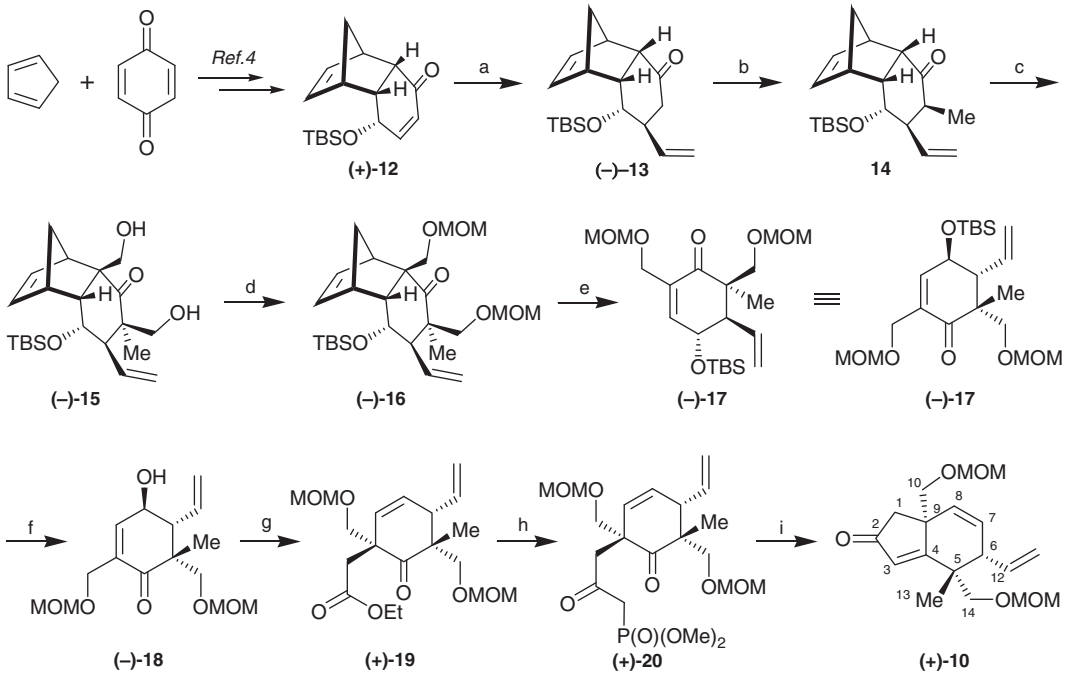
1,4-Addition of vinyl group to the enone moiety of (+)-**12** occurred exclusively from its convex face to furnish **13** as a single diastereomer.[5] The vinyl group was introduced to serve as a latent carboxylic acid equivalent at an appropriate stage. Kinetically controlled methylation in **13** was regiospecific and furnished **14** with good diastereoselectivity (β:α = 9:1), Scheme 2. A single-pot, double hydroxyl-methylation on **14** was expectedly *exo*-face stereoselective and furnished a single diol (−)-**15** in which the key C5 quaternary center and relative stereochemistry at C5 and C6 of the natural product was correctly installed. The two hydroxyl groups in (−)-**15** were protected as MOM derivatives (−)-**16** and a retro Diels–Alder reaction released the functionalized cyclohexenone (−)-**17**, Scheme 2. Selective TBS deprotection in (−)-**17** to (−)-**18** sets the stage for the installation of the key C9 quaternary center with the required relative stereochemistry through a [3.3]-sigmatropic rearrangement. In the event, an Ireland-Claisen protocol was implemented and the desired **(+)-19** was realized, albeit in very modest yield. Stage was now set for the annulation of the five membered ring A on **(+)-19** and this was sought to be achieved through an intramolecular Horner–Wadsworth–Emmons (HWE) reaction.[2b] Consequently, **(+)-19** was homologated to the β-ketophosphonate **(+)-20**, Scheme 2. Intramolecular HWE in the presence of sodium hydride delivered the desired bicyclic AB ring fragment **(+)-10** envisaged in the retrosynthetic theme, Scheme 1. Termination of the surrogacy of the vinyl group as the carboxylic acid equivalent and MOM deprotection in **(+)-10** should lead to the installation of γ-lactone moiety (ring C) on the bicyclic AB core.

Attention was now directed toward the BC ring fragment **11** with the intent to demonstrate the feasibility of installing the γ-lactone moiety in a stereochemically secured manner. In this endeavor, dithiane was identified as the carboxylic acid surrogate. Allylation of chiral synthon **(+)-12** furnished (+)-**21** in a regio- and stereoselective manner.[3c] Conjugate 1,4-addition of dithiane to (+)-**21** occurred preferentially from the *exo*-face and the in situ capture of the resulting enolate with methyl iodide delivered (−)-**22** as a single diastereomer having both the dithiane and the methyl group *cis*-disposed on the convex face, Scheme 3. After considerable trials,[6,7] it was possible to induce dithiane unmasking in (−)-**22** using CAN under controlled conditions to furnish aldehyde (+)-**23**. On α-hydroxymethylation, (+)-**23** directly delivered (−)-**24** through concomitant lactol formation and concurrently secured the C5 quaternary center, Scheme 3. PCC-oxidation of lactol (−)-**24** proceeded smoothly to deliver the lactone (−)-**25**. TBS-deprotection in (−)-**25** to (+)-**26** and further PCC oxidation proved quite eventful and directly delivered (+)-**28**, bearing the requisite hydroxyl-γ-lactone moiety, possibly through the intermediate chromate ester **27**, Scheme 3. Retro-Diels–Alder reaction on (+)-**28** proceeded as planned to disengage the cyclopentadiene moiety and delivered the bicyclic fragment (+)-**29**. Lastly, stereoselective hydride reduction on (+)-**28** under Luche protocol[8] led to **11** with required C7 relative stereochemistry corresponding to the BC ring fragment identified in the retrosynthetic planning.

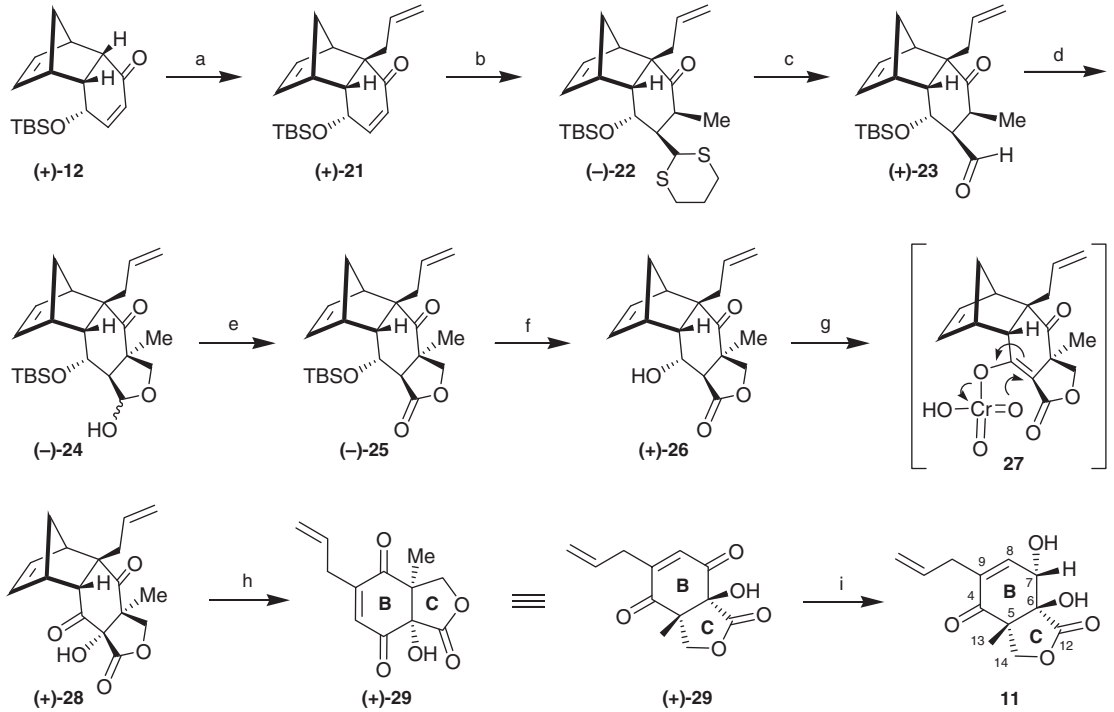
In summary, we have outlined a stereo and enantioselective model study toward complex *seco*-prezizaane natural products from a readily available Chiron. This study has led to the acquisition of key bicyclic AB and BC ring fragments in a concise and stereoselective manner. Our results not only set the stage for executing a general synthesis of *seco*-prezizaane family but offer avenues for exploring the diversity space around these exceptionally bioactive natural products. Efforts along these lines are currently underway in our laboratory.



Scheme 1. Retrosynthesis leading to model fragments.



Scheme 2. Reagents and conditions: (a) Vinylmagnesium bromide, $CuBr{\cdot}SMe_2$, TMSCl, HMPA, THF, −78 to −60 °C, 3 h, 85%; (b) LHMDS, HMPA, MeI, THF, −78– 0 °C, 2 h, 77%; (c) DBU, formalin, THF, 25 °C, 10 h, 60%; (d) MOMCl, DIPEA, DCM, 25 °C, 12 h, 88%; (e) Ph_2O, 210 °C, 15 min, 90%; (f) TBAF, AcOH, THF, 0–25 °C, 2 h, 85%; (g) triethylorthoacetate, propionic acid (0.2 equiv), 190–200 °C, 40 h, 30%; (h) $CH_3P(O)(OCH_3)_2$, *n*-BuLi, THF, −78 °C, 1 h, 95%; (i) NaH, THF, reflux, 2 h, 92%.



Scheme 3. Reagents and conditions: (a) LiHMDS, allyl bromide, HMPA, THF, −20 °C, 2 h, 93%; (b)1,3-dithiane, *n*-BuLi, HMPA, THF, −78 °C, MeI, 3 h, 60%; (c) CAN, CH_3CN, H_2O, 30%; (d) DBU, formalin, THF, 25 °C, 14 h, 60%; (e) PCC, NaOAC, silica, 15 h, 70%; (f) TBAF, THF, 0–25 °C, 2 h, 80%; (g) PCC, NaOAC, silica, 0–25 °C, 1 h, 60%; (h) Ph_2O, 200 °C, 10 min, 75%; (i) $NaBH_4$, $CeCl_3$, −78 °C, 68%.

Acknowledgments

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5. All new compounds were characterized on the basis of their spectroscopic data (IR, ^{1}H, ^{13}C, MS). Spectral data for some of the key compounds are as follows: Compound **15**: $[\alpha]_D^{25}$ −28.3 (*c* = 0.6, $CHCl_3$); IR (neat) 3553, 3071, 1686 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38–6.36 (m, 1H), 5.95–5.93 (m, 1H), 5.73–5.61 (m, 1H), 5.12 (dd, *J* = 9.9 & 1.8 Hz, 1H), 4.98 (dd, *J* = 16.8 & 1.8 Hz, 1H), 4.75 (dd, *J* = 11.1 & 7.2 Hz, 1H), 4.31 (d, *J* = 9.6 Hz, 1H), 3.63–3.49 (m, 3H), 3.26 (s, 1H), 2.99 (bs, 1H), 2.88 (s, 1H), 2.71 (dd, *J* = 7.2 & 3.0 Hz, 1H), 2.21 (t, *J* = 10.5 Hz, 1H), 1.47 (d, J= 8.7 Hz, 1H), 1.39 (d, J = 8.7 Hz, 1H), 0.92 (s, 9H), 0.79 (s, 3H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.09, 138.74, 137.24, 134.95, 118.98, 73.15, 70.47, 70.04, 61.19, 53.16, 52.93, 52.10, 50.29, 48.62, 46.12, 26.04, 26.01, 19.72, 18.21, -3.87, -4.33; LRMS(ES): *m*/*z* calcd for $C_{22}H_{36}NaO_4Si$ (M+Na): 415, found: 415. Compound **17**: $[\alpha]_D^{25}$ −98.3 (*c* = 1.2, $CHCl_3$); IR (neat) 1670, 1471, 1151, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 5.80–5.68 (m, 1H), 5.25–5.12 (m, 2H), 4.74–4.70 (m, 1H), 4.66 (s, 2H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.46 (d, *J* = 6.6 Hz, 1H), 4.21 (s, 2H), 3.59 (d, *J* = 9.3 Hz, 1H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.37 (s, 3H), 3.27 (s, 3H), 2.50 (t, *J* = 9.3 Hz, 1H), 1.06(s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.90, 148.18, 135.08, 134.20, 120.49, 96.51, 96.26, 72.20, 68.45, 64.22, 57.70, 55.34, 49.13, 25.79, 19.99, 18.06, -4.29, -4.39; HRMS(ES): *m*/*z* calcd for $C_{21}H_{38}NaO_6Si$ (M+Na): 437.2335, found: 437.2338. Compound **19**: $[\alpha]_D^{25}$ +51.7 (*c* = 0.6, $CHCl_3$); IR (neat) 2933, 1736, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.71 (m, 3H), 5.19–5.13 (m, 2H), 4.57–4.53 (m,4H), 4.10–4.03 (m, 2H), 3.81 (d, *J* = 9.6 Hz, 1H), 3.65 (d, *J* = 9.3 Hz, 1H), 3.48–3.42 (m, 2H), 3.32 (s, 6H), 3.03 (d, *J* = 15.9 Hz, 1H), 2.59 (d, *J* = 15.3 Hz, 1H), 1.31 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.87, 170.88, 136.52, 130.45, 128.36, 117.83, 96.85, 96.56, 71.95, 70.29, 60.55, 55.48, 55.29, 51.26, 50.10, 48.87, 40.88, 19.66, 14.15. Compound **10**: $[\alpha]_D^{24}$ +107.1 (*c* = 0.8, $CHCl_3$); IR (neat) 3080, 2930, 1719, 1698, 1606, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.88 (dd, *J* = 9.9 & 2.7 Hz, 1H), 5.81–5.69 (m, 1H), 5.59 (dd, *J* = 10.2 &1.8 Hz, 1H), 5.25–5.14 (m, 2H), 4.61–4.53 (m, 4H), 3.84 (d, *J* = 9.6 Hz, 3H), 3.69 (d, *J* = 9.3 Hz, 3H), 3.44–3.28 (m, 8H), 2.82–2.77 (m, 2H), 2.24 (d, *J* = 17.1 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.79, 183.86, 135.51, 131.19, 129.59, 128.64, 118.88, 96.94, 96.61, 73.22, 70.78, 55.70, 55.50, 52.69, 49.73, 49.28, 43.11, 22.24; HRMS (ES): *m*/*z* calcd for $C_{18}H_{26}NaO_5$ (M+Na): 345.1678, found: 345.1677. Compound **22**: $[\alpha]_D^{24}$ -68.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2953, 1695, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23–6.20 (m, 1H), 5.96–5.93 (m, 1H), 5.71–5.57 (m, 1H), 5.10–5.03 (m, 1H), 4.74 (s, 1H), 4.10 (dd, *J* = 9.9 & 7.5 Hz, 1H), 3.13 (s, 1H), 2.91 (s, 1H), 2.86–2.68 (m, 4H), 2.46 (dd, *J* = 6.9 & 3.0 Hz, 1H), 2.13–2.06 (m, 2H), 1.98–1.74 (m, 2H), 1.48 (d, *J* = 8.7 Hz, 1H), 1.38 (d, *J* = 8.7 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.01 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.57, 137.32, 136.78, 134.03, 117.84, 69.88, 59.55, 53.76, 50.83, 49.48, 48.76, 47.74, 46.63, 46.55, 45.96, 33.28, 30.94, 26.89, 25.99, 18.21, 13.73, -3.44, -5.23; HRMS(ES): *m*/*z* calcd for $C_{25}H_{40}NaO_2S_2Si$ (M+Na): 487.2137; found: 487.2135. Compound **25**: $[\alpha]_D^{24}$ -91.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3069, 1794, 1691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37–6.35 (m, 1H), 6.04–6.01 (m, 1H), 5.71–5.57 (m, 1H), 5.15–5.10 (m, 2H), 4.16 (dd, *J* = 11.7 & 6.3 Hz, 1H), 3.97 (d, *J* = 9.1 Hz, 1H), 3.79 (d, *J* = 9.1 Hz, 1H), 3.28 (s, 1H), 3.03 (dd, *J* = 13.2 & 7.5 Hz, 1H), 2.82 (s, 1H), 2.55 (dd, *J* = 6.3 & 3.0 Hz, 1H), 2.34 (d, *J* = 11.1 Hz, 1H), 2.05 (dd, *J* = 12.9 & 8.1 Hz, 1H), 1.66–1.56 (m, 2H), 1.23 (s, 3H), 0.95 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.73, 175.22, 137.86, 134.92, 133.98, 119.09, 71.83, 67.08, 59.46, 55.55, 52.18, 50.47, 50.15, 45.50, 44.89, 25.84, 22.12, 18.06, -4.54, -4.99; HRMS(ES): *m*/*z* calcd for $C_{23}H_{34}NaO_4Si$ (M+Na): 425.2124; found: 425.2125. Compound **28**: $[\alpha]_D^{21}$ +130.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3434, 1780, 1691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21–6.18 (m, 1H), 6.03–6.00 (m, 1H), 5.87–5.73 (m, 1H), 5.15–5.05 (m, 2H), 4.56 (s, 1H), 4.55 (d, *J* = 8.7 Hz, 1H), 4.18 (d, *J* = 9.0 Hz, 1H), 3.53 (s, 1H), 3.28 (s, 1H), 3.04 (d, *J* = 3.9 Hz, 1H), 2.68 (dd, *J* = 15.0 & 7.5 Hz, 1H), 2.46 (dd, *J* = 15.0 & 7.5 Hz, 1H), 2.04 (s, 1H), 1.65 (d, *J* = 12.9 Hz, 1H), 1.49 (d, *J* = 9.3 Hz, 1H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.64, 230.81, 172.46, 139.03, 138.19, 132.32, 119.03, 100.52, 80.13, 63.36, 59.46, 55.89, 50.40, 44.92, 44.36, 43.97, 13.70; HRMS(ES): *m*/*z* calcd for $C_{17}H_{18}NaO_5$ (M+Na): 325.1052; found: 325.1046. Compound **29**: $[\alpha]_D^{21}$ +33.6 (*c* = 1.1, $CHCl_3$); IR (neat) 3446, 1790, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (s, 1H), 5.83–5.70 (m, 1H), 5.34–5.15 (m, 2H), 4.98 (d, *J* = 8.7 Hz, 1H), 4.60 (s, 1H), 4.25 (d, *J* = 8.7 Hz, 1H), 3.20 (d, *J* = 6.6 Hz, 2H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.64, 191.10, 170.63, 154.02, 134.95, 131.30, 120.25, 78.81, 73.76, 58.61, 33.89, 14.36.
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