Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2621–2625

Protecting group directed ring-closing metathesis (RCM): the first total synthesis of an anti-malarial nonenolide

Debendra K. Mohapatra,[a,*] Dhondi K. Ramesh,[a] Michael A. Giardello,[b] Mukund S. Chorghade,[a] Mukund K. Gurjar[a] and Robert H. Grubbs[c,*]

[a]*Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India*
[b]*Materia Inc., 60, N. Gabriel Boulevard, Pasadena, 91107, USA*
[c]*Arnold and Mable Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, 91125, USA*

Received 21 December 2006; revised 23 January 2007; accepted 1 February 2007
Available online 15 February 2007

Abstract—The first synthesis of a newly found naturally occurring anti-malarial nonenolide is described. A pivotal step in the synthesis is the ring-closing metathesis of a dienoic ester prepared by coupling an acid and alcohol that were stereoselectively synthesized from (*S*)-α-hydroxy-γ-butyrolactone and 1,2-*O*-isopropylidene D-glyceraldehyde, respectively.

Natural resources such as plants, animals, and microorganisms constitute a rich and versatile source of bioactive chemicals; many of them and their synthetic derivatives have been proven to be beneficial to human health. Much current interest has been focused on the utility of naturally occurring bifidus factors and growth inhibitors against harmful bacteria such as *Clostridium* and *E. coli*. The ascomycetous genus *Cordyceps* is an entomopathogenic fungus that has found extensive use in food and herbal medicines in Asia.[1] The approximately 400 species of *Cordyceps* known so far are distinguished from each other and classified according to the color and shape of their fruiting bodies, possession of spores, ascus shape, host insect species, and by other morphological characteristics.[2]

Cordyceps militaris, an enthomopathogenic fungus belonging to the class *Ascomycetes*, adheres to the surface of insects during the winter, followed by penetration of its body by a fruiting body and sporangium.[3] Reports on the isolation of biologically active secondary metabolites from *C. militaris* have been sparse.[4] In recent years, these secondary metabolites have received attention due to their unique structures and specific biological activities. Cordycepins (3′-deoxyadenosine), possessing antifungal, antivirus, and antitumor activities, is one of a number of selected secondary metabolites that have been previously isolated from *C. militaris*.[4a,5] Compound **1** was recently isolated as a white solid from *C. militaris* BCC 2816; the structure was elucidated and the stereochemistry confirmed by spectral data and X-ray crystallographic analysis.[6]

As part of our ongoing program on the synthesis of natural lactones[7] with ring-closing metathesis (RCM)[8,9] as a key step, we have devised a stereoselective synthesis of nonenolide **1**. Despite its effectiveness in the synthesis of rings of all sizes, two factors still limit the scope of the RCM reaction: (a) in ring sizes $\geqslant 8$, control over *E*/*Z* stereochemistry of the double bond generated is difficult and not demonstrated. Stereochemical control is probably of thermodynamic origin;[10] (b) reports that describe the application of RCM to medium sized, particularly 10-membered rings, are still rare, especially when dense functionality close to the reaction center is involved.[11] A dearth of reports on RCM reactions on substrates wherein chiral centers with protecting groups are present adjacent to both the reacting sites (Fig. 2), prompted us to investigate the outcome of such RCM reactions with promise in the synthesis of nonenolides with chiral centers on both sides of the double bond (Fig. 1).

Keywords: Nonenolide; Anti-malarial agent; 1,2-*O*-Isopropylidene D-glyceraldehyde; Yamaguchi esterification; Ring-closing metathesis.
* Corresponding authors. Tel.: +91 20 25902627; fax: +91 20 25902629 (D.K.M.); e-mail: dk.mohapatra@ncl.res.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.040

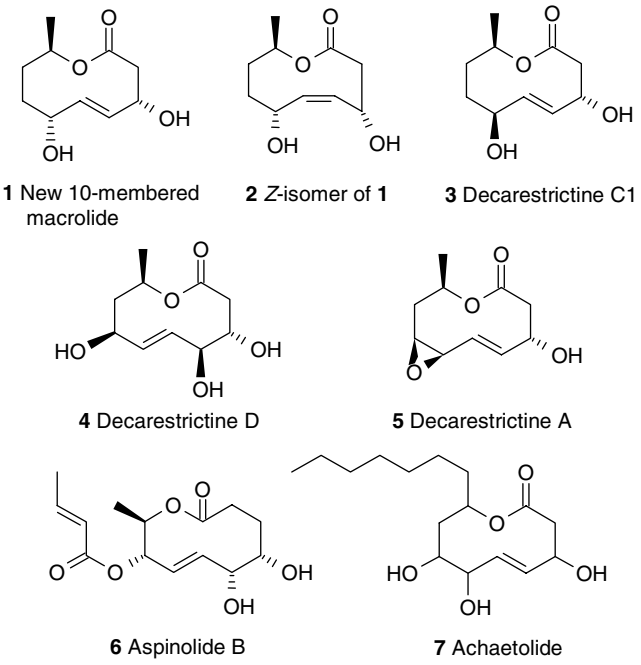


Figure 1. Some natural nonenolides with chiral centers on both sides of the double bond.

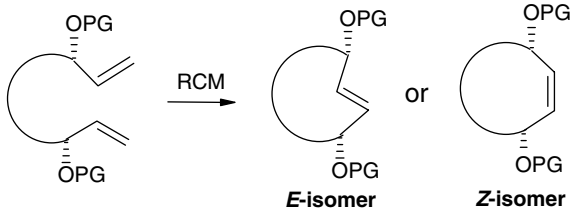
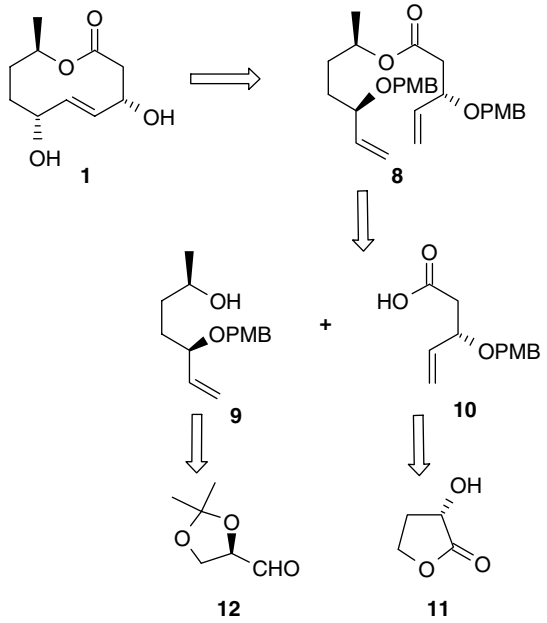


Figure 2. Outcome of the RCM reaction.



Scheme 1. Retrosynthetic analysis.

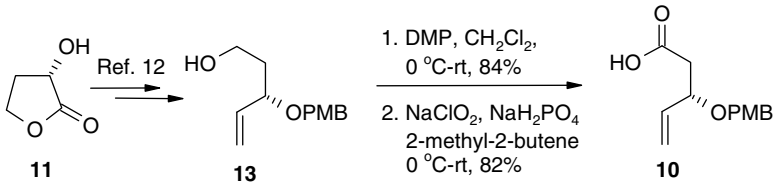
Our retrosynthetic analysis is depicted in Scheme 1. The macrolactonization step relies on the RCM reaction on a diolefinic ester. Strategic bond disconnection in ester **8** leads to chiral, nonracemic fragments **9** and **10** that could be derived from (*S*)-α-hydroxy-γ-butyrolactone (**11**) and 1,2-*O*-isopropylidene D-glyceraldehyde (**12**), respectively.

Synthesis of acid component **10** began with **13** prepared by a literature procedure.[12] The spectroscopic and analytical data {$[\alpha]_D^{25}$ −54.8 (*c* 1.0, $CHCl_3$); lit.[12] $[\alpha]_D^{25}$ −56.0 (*c* 1.42, $CHCl_3$)} of **13** were in excellent agreement with that reported. The primary hydroxyl group was then oxidized with Dess–Martin periodinane (DMP)[13] to afford the corresponding aldehyde; further treatment with $NaClO_2$[14] in the presence of NaH_2PO_4 and 2-methyl-2-butene as a scavenger gave the required acid **10** in 82% overall yield[15] (Scheme 2).

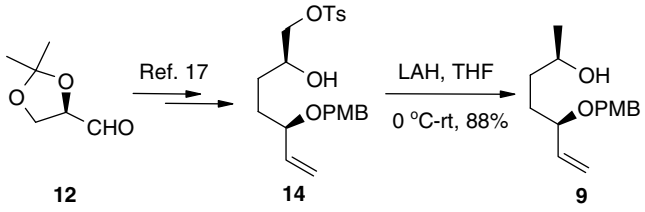
Compound **9**[16] was obtained in twelve steps and 26% overall yield, from 1,2-*O*-isopropylidene D-glyceraldehyde (**12**), following a standard protocol[17] (Scheme 3).

Our next task was to couple the two fragments and conduct the critical RCM reaction. Carboxylic acid **10** was coupled with alcohol **9** under Yamaguchi's protocol[18] (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) to afford diene ester **8**[19] in 89% yield (Scheme 4). This set the stage for the crucial ring-closing metathesis, which was successfully achieved with Grubbs' second-generation catalyst **17**. The extent of bias, if any, conferred by the protecting groups on the stereochemistry of the newly formed double bond is not readily obvious and cannot be predicted with certainty. We envisaged that PMB-protecting groups around the reacting centers might act as temporary constraints to adequately shape this particular diene and simultaneously confer selectivity upon the stereochemistry of the newly formed double bond: we were pleased to observe this. A 0.001 M solution of **8** and 10 mol % of Grubbs' second-generation catalyst **17** was heated at reflux for 8 h in dry, degassed CH_2Cl_2. This provided the desired 10-membered macrolactone (*E*)-**15** as the major product in 78% yield. We were unable to ascertain the precise *E*/*Z* ratio. Deprotection of the PMB groups yielded natural product **1** in 92% yield together with a small amount of (*Z*)-isomer (**2**) (*E*/*Z* = 90:10). The geometry of the newly formed double bond in the major product was unequivocally assigned by detection of the olefinic J_{trans} coupling constant (15.9 Hz between the protons at δ 5.61 and 5.73 ppm, respectively). The specific rotation does, indeed, deviate a little, but, more importantly, it is close to the reported value and of the same sign {$[\alpha]_D^{25}$ −49.8 (*c* 0.30, MeOH); lit.[6] $[\alpha]_D^{25}$ −55.0 (*c* 0.036, MeOH)}. The constitution and configuration of the assigned compounds are unambiguous as the NMR and elemental analysis were in excellent accord with the proposed structure and perfectly matched those reported in the literature.[6,20]

To verify the effect of the PMB group upon the stereochemistry of the newly formed double bond, we carried out the RCM reaction with diol **16** after deprotection of



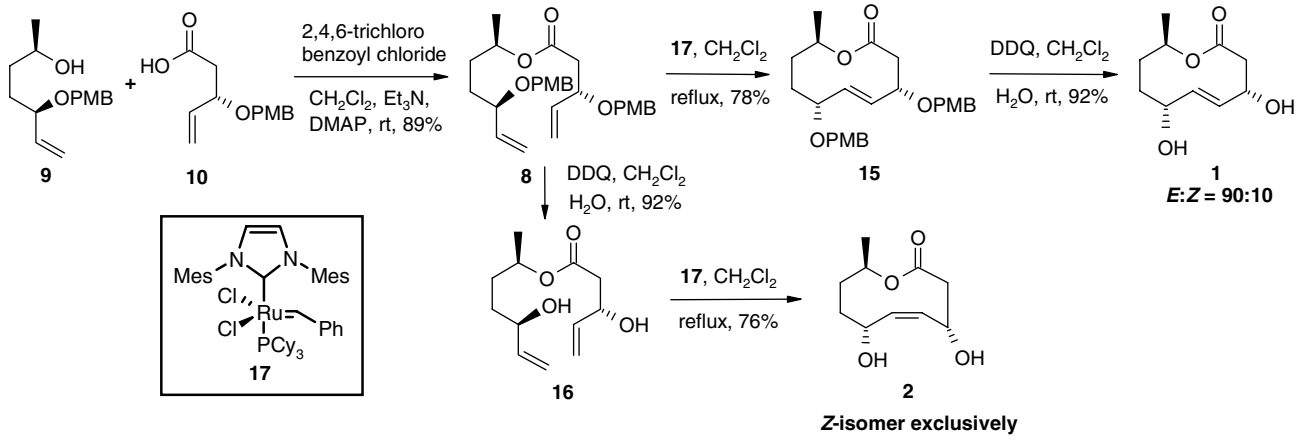
Scheme 2. Synthesis of acid **10**.



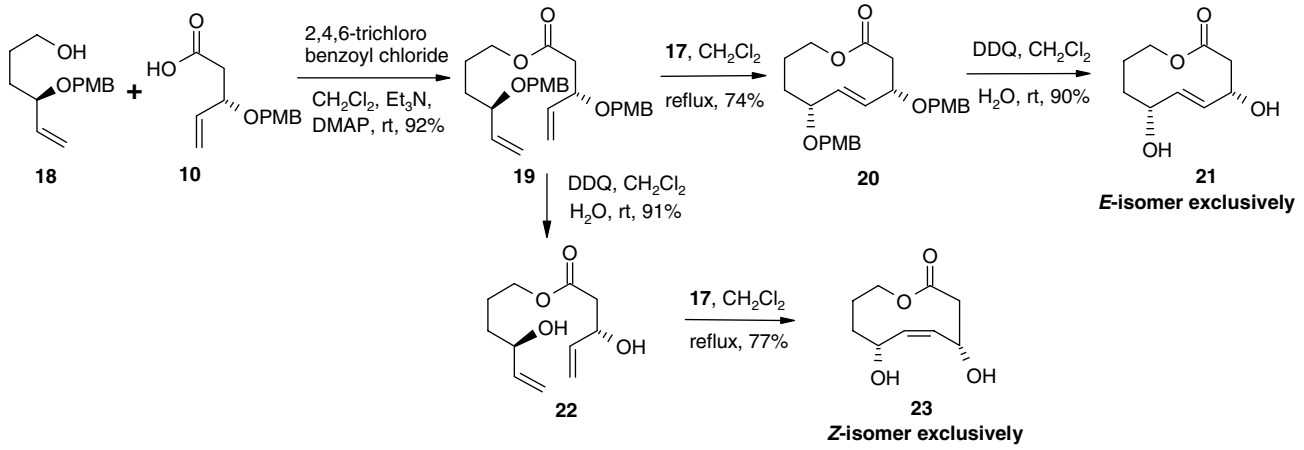
Scheme 3. Synthesis of alcohol **9**.

the PMB groups of **8**. The RCM reaction on **16** (0.001 M in CH_2Cl_2) with Grubbs' second-generation catalyst (10 mol %) afforded the 10-membered lactone **2**[21] as the sole product in 76% yield. We were surprised to find that the newly formed double bond had the *Z* conformation as evidenced by the coupling constant of 11.2 Hz. No chromatographic or spectroscopic evidence for the formation of the *E* isomer was discernible.

Next, we wanted to verify the consistency of the results obtained from the RCM reactions depicted above. Thus, acid **10** was coupled with (*R*)-4-*p*-methoxybenzylhex-5-en-1-ol (**18**) to afford ester **19** under Yamaguchi conditions in 92% yield. The RCM reaction, as before, and deprotection of the PMB groups furnished the 10-membered lactone **21** with the *E* isomer as the only product (Scheme 5). Similarly, RCM reaction on diol **22** afforded exclusively *Z* isomer **23** in 77% yield, the structure and



Scheme 4. Synthesis of an anti-malarial nonenolide **1** and its *Z*-isomer **2**.



Scheme 5. Synthesis of desmethyl nonenolide **21** and its *Z*-isomer **23**.

stereochemistry, were unambiguously established by ^{1}H and ^{13}C NMR analysis.

In summary, a concise first total synthesis of the *E* and *Z* isomers of the potent anti-malarial **1** and related congeners is presented. Our success was based on synthesizing two coupling partners from inexpensive, commercially available starting materials and exploiting a diastereoselective ring-closing metathesis for the formation of the 10-membered lactone ring. Extension of this protocol to other members of this series and to different ring sized derivatives is underway and will be disclosed in due course.

Acknowledgments

D.K.R. thanks the CSIR, New Delhi, for financial support in the form of a research fellowship. We also thank Dr. P. R. Rajmohanan for the NMR data, respectively.

References and notes

1. (a) Huang, L. F.; Liang, Y. Z.; Guo, F. Q.; Zhou, Z. F.; Chang, B. M. *J. Pharm. Biomed. Anal.* **2003**, *33*, 1155–1162; (b) Weng, S. C.; Chou, C. J.; Lin, L. C.; Tsai, W. J.; Kuo, Y. C. *J. Ethnopharmacol.* **2002**, *83*, 79–85.
2. (a) Isaka, M.; Kittakoop, P.; Kirtikara, K.; Hywel-Jones, N. L.; Thebtaranonth, Y. *Acc. Chem. Res.* **2005**, *38*, 813–823, and references cited therein; (b) Shimazu, D. *Color Iconography of Vegetable Wasps and Plant Worms*; Seibundo Shinkosha: Tokyo, 1994; (c) Bowman, B. H.; Taylor, J. W.; Brownlee, A. G.; Lee, J.; Lu, S. D.; White, T. J. *Mol. Biol. Evol.* **1992**, *9*, 285–296; (d) Barbee, M. L.; Taylor, J. W. *Mol. Biol. Evol.* **1992**, *9*, 278–284.
3. Seung, J. M. *Codyceps of Korea*; Kyo-Hak Publishing: Seoul, Korea, 1996; pp 22–167.
4. (a) Bentley, H. R.; Cunningham, K. G.; Spring, F. S. *J. Chem. Soc.* **1951**, 2301–2305; (b) Cunningham, K. G.; Hutchinson, S. A.; Manson, W.; Spring, F. S. *J. Chem. Soc.* **1951**, 2299–2300.
5. Kredich, N. M.; Guarino, A. *J. Biochim. Biophys. Acta* **1960**, *41*, 363–371.
6. Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953–1955.
7. (a) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V.; Karmakar, S.; Mohapatra, D. K. *Arkivoc* **2005**, *3*, 237–257; (b) Mohapatra, D. K.; Yellol, G. S. *Arkivoc* **2005**, *3*, 144–155; (c) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525–4526; (d) Mohapatra, D. K.; Durugkar, K. A. *Arkivoc* **2004**, *1*, 146–155; (e) Mohapatra, D. K.; Yellol, G. S. *Arkivoc* **2003**, *9*, 21–33.
8. For a discussion of strategic advantages related to RCM, see: Fürstner, A. *Synlett* **1999**, 1523–1533.
9. (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (c) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830; (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (f) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077; (g) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (h) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.
10. (a) Bourgeios, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869–882; (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
11. (a) Sharma, G. V. M.; Cherukupallu, G. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1081–1088, and references cited therein; (b) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069; (c) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671–672; (d) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Montio, D.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 9187–9190; (e) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New. J. Chem.* **2001**, *25*, 1347–1350; (f) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287–3289; (g) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4060–4062; (h) Mendez-Andino, J.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1263–1265; (i) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. *Heterocycles* **2000**, *53*, 301–308; (j) Bamford, S. J.; Goubitz, K.; Van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 345–351; (k) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798–4816; (l) Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 7765–7768; (m) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041–1042; (n) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334–4344; (o) Gerlach, K.; Quitschalle, M.; Kalesse, M. *Synlett* **1998**, 1108–1110; (p) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757–4760; (q) Fürstner, A.; Müller, T. *Synlett* **1997**, 1010–1012.
12. White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142.
13. (a) Dess, B. D.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (b) Dess, B. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
14. Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569.
15. Analytical and spectral data of **10**. $[\alpha]_D^{25}$ −32.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.48 (dd, 1H, $J = 5.2$, 16.0 Hz), 2.63 (dd, 1H, $J = 8.0$, 16.0 Hz), 3.79 (s, 3H), 4.22 (m, 1H), 4.30 (d, 1H, $J = 11.2$ Hz), 4.52 (d, 1H, $J = 11.2$ Hz), 5.27–5.37 (m, 2H), 5.78 (m, 1H), 6.82–6.87 (m, 2H), 7.20–7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.9, 55.1, 70.2, 76.2, 113.8, 118.3, 129.4, 130.0, 137.0, 159.2, 176.5. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.91; H, 6.75.
16. Analytical and spectral data of **9**. $[\alpha]_D^{25}$ +19.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (d, 3H, $J = 6.0$ Hz), 1.44–1.58 (m, 2H), 1.62–1.69 (m, 2H), 2.10 (br s, 1H) 3.70–3.77 (m, 2H), 3.80 (m, 3H), 4.24 (d, 1H, $J = 11.3$ Hz), 4.50 (d, 1H, $J = 11.3$ Hz), 5.16–5.26 (m, 2H), 5.76 (m, 1H), 6.84–6.88 (m, 2H), 7.21–7.27 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3, 31.7, 34.9, 55.1, 67.5, 69.7, 80.2, 113.7, 117.0, 129.3, 130.4, 138.8, 159.0. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found C, 71.94; H, 8.72.
17. Rama Rao, A. V.; Murthy, V. S.; Sharma, G. V. M. *Tetrahedron Lett.* **1995**, *36*, 139–142.
18. Inanga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; Okino, T.; Qi, S.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *J. Nat. Prod.* **1997**, *60*, 158–161.
19. Analytical and spectral data of **8**. $[\alpha]_D^{25}$ +8.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.16 (d, 3H, $J = 6.3$ Hz), 1.55–1.61 (m, 4H), 2.38 (dd, 1H, $J = 5.8$, 15.0 Hz), 2.56 (dd, 1H, $J = 8.0$, 15.0 Hz), 3.64 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.20 (m, 1H), 4.28 (d, 2H, $J = 11.3$ Hz), 4.46 (d, 2H, $J = 11.3$ Hz), 4.89 (m, 1H), 5.13–5.33 (m, 4H), 5.59–5.85 (m, 2H), 6.81–6.87 (m, 4H), 7.19–7.27 (m, 4H); ^{13}C

NMR (50 MHz, $CDCl_3$): δ 20.0, 31.3, 31.7, 41.3, 55.0, 69.7, 70.1, 71.0, 76.7, 79.8, 113.6, 117.1, 117.7, 129.2, 130.3, 130.6, 137.4, 138.9, 159.0, 170.2. Anal. Calcd for $C_{28}H_{36}O_6$: C, 71.77; H, 7.74. Found: C, 71.68; H, 7.64.

20. Analytical and spectral data of **1**. $[\alpha]_D^{25}$ Found: −49.8 (*c* 0.3, MeOH); lit: −55.0 (*c* 0.036, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ 1.14 (d, 2.7H, $J = 6.5$ Hz), 1.18 (d, 0.3H, $J = 6.8$ Hz, cis), 1.57–1.64 (m, 2H), 1.77 (m, 1H), 1.95 (m, 1H), 2.04 (dd, 0.1H, $J = 6.4$, 13.8 Hz, cis), 2.30 (dd, 0.1H, $J = 6.4$, 13.8 Hz, cis), 2.46 (dd, 0.9H, $J = 3.5$, 11.9 Hz), 2.51 (dd, 0.9H, $J = 3.7$, 11.9 Hz), 2.93 (dd, 0.1H, $J = 7.6$, 13.8 Hz, cis), 4.11 (m, 1H), 4.63 (m, 1H), 4.78 (m, 1H), 5.61 (ddd, 1H, $J = 1.3$, 8.4, 15.9 Hz), 5.73 (dd, 1H, $J = 3.0$, 15.9 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 20.6, 29.4 (cis), 31.3, 31.7 (cis), 44.0, 66.8, 70.7 (cis), 72.9, 74.3, 130.4, 133.0, 170.3. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05; Found: C, 59.87; H, 8.02.

21. Analytical and spectral data of **2**. $[\alpha]_D^{25}$ −28.0 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 1.22 (d, 3H, $J = 3.1$ Hz), 1.35–1.43 (m, 2H), 1.71 (m, 1H), 2.00 (m, 1H), 2.08 (dd, 1H, $J = 11.0$, 14.2 Hz), 2.83 (dd, 1H, $J = 5.9$, 14.2 Hz), 4.67 (m, 1H), 4.84 (m, 1H), 4.98 (m, 1H), 5.24 (m, 1H), 5.35 (dd, 1H, $J = 9.3$, 11.2 Hz); ^{13}C NMR (125 MHz, CD_3OD): δ 17.1, 30.7, 43.8, 65.2, 67.0, 71.8, 133.4, 134.3, 170.9. Anal. Calcd for $C_{10}H_{16}H_4$: C, 59.98; H, 8.05. Found: C, 59.79; H, 8.12.