Tetrahedron Letters 50 (2009) 3063–3066

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new approach to A/B ring analogue of eleutherobin and sarcodictyns through a sequence of highly diastereofaceselective Diels–Alder reaction and ring opening–ring closing metathesis (RO–RCM)

Chanchal K. Malik, Md. Firoj Hossain, Subrata Ghosh *

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

ARTICLE INFO

Article history:
Received 27 February 2009
Revised 2 April 2009
Accepted 3 April 2009
Available online 14 April 2009

Keywords:
Diels–Alder reactions
Metathesis
Oxygen heterocycles
Terpenes

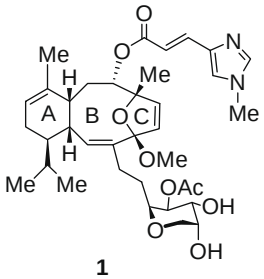
ABSTRACT

An approach to the construction of A/B ring analogue of antitumour compounds eleutherobin and sarcodictyns is described. The key steps involve a highly diastereofaceselective Diels–Alder reaction of a dienophile containing a furanosugar moiety with cyclopentadiene and ring opening–ring closing metathesis of the resulting adduct.

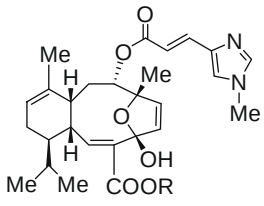
Eleutherobin **1**[1] and sarcodictyns A **2**[2] and B **3** are marine diterpenoids that possess a common oxa-bridged tricyclic skeleton **4** as the core structure. These compounds exhibit potent antitumour activities against a variety of tumour cells. Interestingly these compounds display cytotoxic action through a paclitaxel-like mechanism.[3] Because of complex molecular architecture and scarce availability, these compounds have elicited considerable interest in developing efficient routes for their total synthesis as well as for synthesis of structurally simpler analogues. These efforts have resulted in a number of elegant approaches[4] towards the construction of the core structure culminating in the total synthesis of sarcodictyns and eleutherobin (Scheme 1) by the groups of Nicolaou[5] and Danishefsky.[6]

A major challenge in the synthesis of these natural products is the construction of the oxa-tricyclic core structure **4**. The majority of the approaches reported so far involve annulation of a medium-sized carbocycle onto carvone-derived compounds followed by oxa-bridge formation intramolecularly. We thought of developing a conceptually new approach that offers a possibility of generating simultaneously the A/B ring system of eleutherobin and sarcodictyns. Our retrosynthetic analysis (Scheme 2) identified the fused tricyclic nine-membered lactone **6** as the key intermediate which could in principle be elaborated to the core structure **4** through RCM of the divinyl compound **5**.[7] The tricyclic lactone **6** is expected to be available from RO–RCM of the bicyclo[2.2.1]heptene derivative **7** after modification of the carbocyclic ring to the desired six-membered one. A Diels–Alder reaction of the dienophile **8** with an appropriately functionalized cyclopentadiene derivative would provide **7**. Preliminary results of the investigation based on this concept resulting in the synthesis of A/B ring analogue of eleutherobin and sarcodictyns are presented here.

Two crucial steps on which success of this strategy depends are the selectivity of the proposed Diels–Alder reaction of the enone with a pendant sugar residue and RO–RCM of the resulting adduct. Although RO–RCM[8] of appropriately constructed bicyclo[2.2.1]-heptenes has been investigated to construct fused- and bridged-cyclic systems containing medium-sized carbocyclic ring, there is no report on the synthesis of fused bicycles with nine-membered lactone through RO–RCM. Indeed there are only few reports where



1

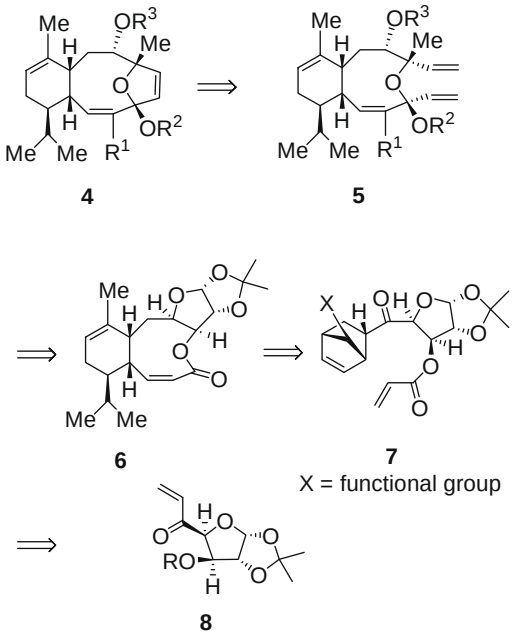


2, R = Me
3, R = Et

Scheme 1.

* Corresponding author. Tel.: +91 33 2473 4971; fax: +91 33 2473 2805.
E-mail address: ocsg@iacs.res.in (S. Ghosh).

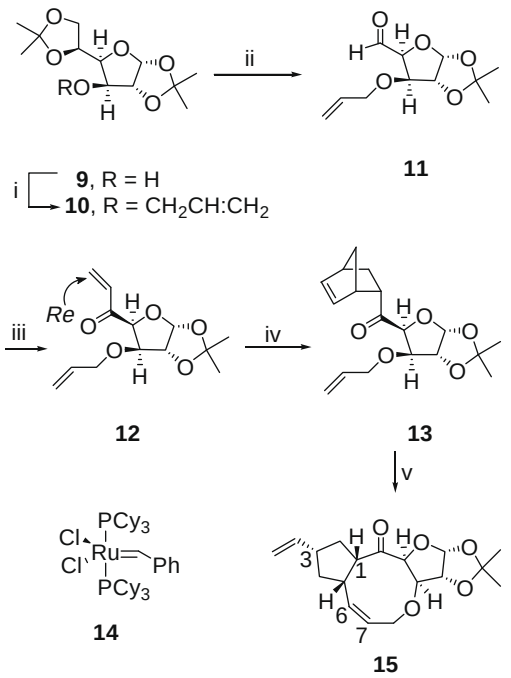
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.033



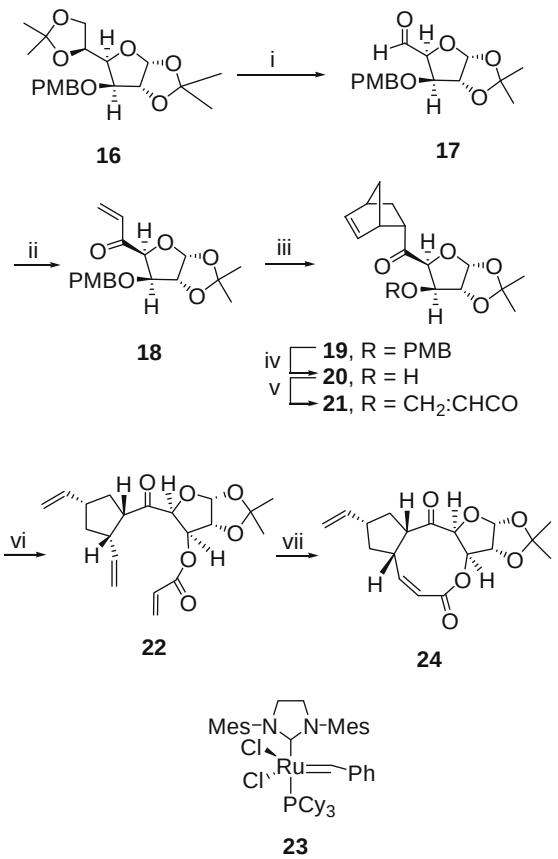
Scheme 2.

RCM has been employed to construct nine-membered lactones.[9] To determine the stereoselectivity in the Diels–Alder reaction of the enone **8** and the efficiency of the RO–RCM reaction of the resulting bicyclo[2.2.1]heptene, we initially chose to employ the above-mentioned protocol for synthesis of a fused bicycle with a nine-membered cyclic ether. The dienophile required for this purpose was prepared as described in Scheme 3. The hydroxyl group in diacetone glucose **9** was converted to the allyl ether **10**[4j] on reaction of its sodium salt with allyl bromide. Selective removal of the 5,6-acetonide moiety and periodate cleavage of the vicinal diol resulted in the known aldehyde **11**.[4j] Reaction of this aldehyde with vinyl magnesium bromide followed by oxidation of the carbinol produced the enone **12** in overall excellent yield. Diels–Alder reaction of the enone **12** with cyclopentadiene in the presence of anhydrous $ZnCl_2$ as catalyst was found to be highly diastereoselective producing exclusively the adduct **13** in 95% isolated yield arising through addition of the diene to the *Re*-face of the dienophile. The structure of this adduct was established in analogy to the formation of the adduct **19** on reaction of the analogous dienophile **18** with cyclopentadiene (Scheme 4). The adduct **13** was then subjected to metathesis with Grubbs' first generation catalyst **14** in the presence of ethylene at rt. To our delight the fused bicycle **15** containing a nine-membered cyclic ether was obtained in 78% yield. The structure of **15** was established from spectral data.[12] The formation of *Z*-olefin was established from the coupling constant (J = 10.5 Hz) of the C_6- and C_7-olefinic protons at δ 5.51 (dt, J = 4, 10.5 Hz) and 5.57 (dt, J = 2, 10.5 Hz).

With the success of the above-mentioned protocol in synthesizing fused bicycles with a nine-membered cyclic ether, we next embarked upon the synthesis of the bicycle with nine-membered lactone, the projected intermediate for the synthesis of the core structure of eleutherobin and sarcodictyns. The dienophile required for this purpose was prepared in the following way (Scheme 4). Acid-induced deprotection of the 5,6-acetonide moiety of the known glucofuranose derivative **16**[10] followed by periodate cleav-



Scheme 3. Reagents and conditions: (i) NaH, HMPA, THF, CH_2:$CHCH_2Br$, rt, 83%; (ii) (a) 75% aq HOAc, 12 h, 78%, (b) $NaIO_4$, CH_3CN:H_2O (3:1), 2 h, 70% ; (iii) (a) CH_2:CHMgBr, THF, −78 °C to rt, 5 h, 70%, (b) DMP, CH_2Cl_2, 1 h, 90% (iv) cyclopentadiene, $ZnCl_2$, CH_2Cl_2, −78 °C, 5 h, 95%; (v) catalyst **14** (5 mol %), CH_2Cl_2, C_2H_4, rt, 12 h, 78%.



Scheme 4. Reagents and conditions: (i) (a) 75% aq HOAc, 12 h, 80%, (b) $NaIO_4$, CH_3CN : H_2O (3:1), 2 h, 73%; (ii) (a) CH_2:CHMgBr, THF, −78 °C to rt, 5 h, 68%, (b) DMP, CH_2Cl_2, 1 h, 95% (iii) cyclopentadiene, $ZnCl_2$, CH_2Cl_2, −78 °C, 5 h, 92%; (iv) DDQ, CH_2Cl_2 : H_2O (18:1), 4 h, 87%; (v) CH_2:CHCOCl, Et_3N, DMAP (cat.), CH_2Cl_2, 1 h, 85%; (vi) catalyst **14** (5 mol %), CH_2Cl_2, C_2H_4, rt, 2 h, 95%; (vii) catalyst **23** (5 mol %), C_6H_6, 50 °C, 1 h, 65% (based on recovered **22**).

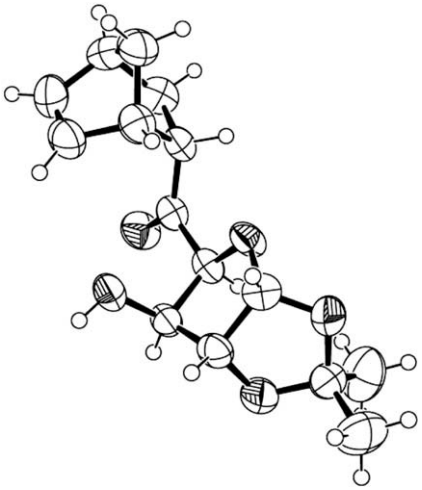


Figure 1. ORTEP diagram of compound **20**.

age of the resulting vicinal diol afforded the aldehyde **17**. Addition of vinyl magnesium bromide to the aldehyde **17** and subsequent oxidation of the carbinol afforded the required enone **18**. Diels–Alder reaction of the enone **18** with cyclopentadiene in the presence of anhydrous $ZnCl_2$ as catalyst was found to be highly diastereoselective producing exclusively the adduct **19** in 92% isolated yield. The structure of the adduct **19** was established by determination of X-ray crystal structure (Fig. 1)[11] of the hydroxy compound **20** obtained through removal of PMB protecting group. The hydroxy compound **20** was then transformed to the ester **21** on reaction with acryloyl chloride. Unlike metathesis of **13**, metathesis of the compound **21** with the catalyst **14** under identical condition gave quantitatively the ring-opened product **22**. However, the ring-opened product **22** could be cyclized using the catalyst **23** to produce the fused bicycle **24** containing nine-membered lactone in 65% yield (based on recovered **22**). The structure of the compound **24** was established through spectral data. The tricycle **24** contains all necessary functional groups for transformation to the core structure of **1**–**3**.

In conclusion we have developed a protocol for convenient access to nine-membered cyclic ether and nine-membered lactone fused to a functionalized cyclopentane ring. The fused bicycle with the nine-membered lactone is a potential intermediate to the synthesis of eleutherobin and sarcodictyns.

Acknowledgements

Financial support from the Department of Science and Technology, Government of India through Ramanna Fellowship to S.G. is gratefully acknowledged. C.K.M. and M.F.H. thank CSIR, New Delhi for Research Fellowships. We thank DST for funds for National Single Crystal Diffractometer facility at the Department of Inorganic Chemistry.

References and notes

1. Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744.
2. (a) D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019; (b) D'Ambrosio, M.; Guerriero, A.; Pietra, R. *Helv. Chim. Acta* **1988**, *71*, 964.
3. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
4. (a) Lindel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 774; (b) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 153; (c) Baron, A.; Caprio, V.; Mann, J. *Tetrahedron Lett.* **1999**, *40*, 9321; (d) Tsypysheva, I. P.; Kunakova, A. M.; Valeev, F. A.; Tolstikov, G. A. *Chem. Nat. Compd.* **2001**, *37*, 490; (e) By, K.; Kelly, P. A.; Kurth, M. J.; Olmstead, M. M.; Nantz, M. H. *Tetrahedron* **2001**, *57*, 1183; (f) Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531; (g) Ceccarelli, S. M.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 7421; (h) Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805; (i) Scalabrino, G.; Sun, X. W.; Mann, J.; Baron, A. *Org. Biomol. Chem.* **2003**, *1*, 318; (j) Kaliappan, K. P.; Kumar, N. *Tetrahedron Lett.* **2003**, *44*, 379; (k) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913; (m) Beumer, R.; Bayon, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59*, 8803; (n) Chandrasekhar, S.; Jagadeshwar, V.; Narsihmulu, C.; Sarangapani, M.; Krishna, D. R.; Vidyasagar, J.; Vijay, D.; Sastry, N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3687; (o) Chiang, G. C. H.; Bond, A. D.; Ayscough, A.; Pain, G.; Ducki, S.; Holmes, A. B. *Chem. Commun.* **2005**, 1860; (p) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2006**, *12*, 51; (q) Dhulut, S.; Bourin, A.; Lannou, M. I.; Fleury, E.; Lensen, N.; Chelain, E.; Pancrazi, A.; Ardisson, J.; Fahy, J. *Eur. J. Org. Chem.* **2007**, 5235.
5. (a) Nicolaou, K. C.; Delft, F. V.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2520; (b) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkom, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353.
6. Chen, X. T.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.
7. Construction of a B/C ring analogue through RCM of an analogous divinyl system has been reported recently. See Ref. 4o.
8. (a) Stragies, R.; Blechert, S. *Synlett* **1998**, 169; (b) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828; (c) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2002**, *58*, 6651; (d) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475; (e) Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5805; (f) Holtsclaw, J.; Koreeda, M. *Org. Lett.* **2004**, *6*, 3719; (g) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094; (h) Maechling, S.; Norman, S. E.; Mckendrick, J. E.; Basra, S.; Koppner, K.; Blechert, S. *Tetrahedron Lett.* **2006**, *47*, 189; (i) Malik, C. K.; Ghosh, S. *Org. Lett.* **2007**, *9*, 2537; (k) Maity, S.; Ghosh, S. *Tetrahedron Lett.* **2008**, *49*, 1133; (l) Mondal, S.; Malik, C. K.; Ghosh, S. *Tetrahedron Lett.* **2008**, *49*, 5649.
9. (a) Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81; (b) Takahashi, T.; Watanabe, H.; Kitahara, T. *Heterocycles* **2002**, *58*, 99; (c) Ramirez-Fernandez, J.; Collado, I. G.; Hernandez-Galan, R. *Synlett* **2008**, 339.
10. Czernecki, S.; Gorson, G. *Tetrahedron Lett.* **1978**, 4113.
11. *Crystal data for compound* ***20***: A plate-shaped colourless crystal ($0.3 \times 0.24 \times 0.08$) was analyzed. $C_{15}H_{20}O_5$, Mr = 280.31, monoclinic, space group P2(1) (no. 4) a = 10.337(4), b = 5.798(2), c = 13.054(5) Å, β = 113.295(5), V = 718.6(5) Å^3, T = 100 K, Z = 2. ρ_{calcd} = 1.295 g cm^{-3}. F (0 0 0) = 300, λ (Mo Kα) = 0.71073 Å, μ Mo Kα/mm^{-1} = 0.097, 3193 reflections measured, 761 observed ($I > 2\sigma$ (I)) 187 parameters; R_{int} = 0.0345, R_1 = 0.0305; wR_2 = 0.0753 ($I > 2\sigma$ (I)), R_1 = 0.0347; wR_2 = 0.0780 (all data) with GOF = 1.045. X-ray single crystal data were collected using Mo Kα (λ = 0.7107 Å) radiation on a SMART APEX diffractometer equipped with CCD area detector. The structure was solved by direct method and was refined in a routine manner. Crystallographic data for compound **20** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 708798. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223-336033. E-mail: deposit@ccdc.cam.ac.uk.
12. All new compounds were characterized on the basis of IR, ^{1}H, ^{13}C NMR and HRMS data. Spectral data for selected compounds: Compound **13**: IR ν_{max} = 1708 cm^{-1} , $[\alpha]_D^{26}$ − 112 (c 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (1H, m), 1.31 (3H, s), 1.37–1.42 (2H, m), 1.45 (3H, s), 1.74–1.82 (1H, ddd, J = 3.6, 8.9, 11.9 Hz), 2.85 (1H, br s), 3.23 (1H, br s), 3.33–3.39 (1H, m), 3.94 (1H, dd, J = 5.8, 12.8 Hz), 4.03 (1H, dd, J = 5.3, 12.7 Hz), 4.19 (1H, d, J = 3.6 Hz), 4.54 (1H, d, J = 3.8 Hz), 4.65 (1H, d, J = 3.6 Hz), 5.16–5.27 (2H, m), 5.74–5.79 (1H, m), 5.83 (1H, dd, J = 2.2, 5.4 Hz), 6.05 (1H, d, J = 3.6 Hz), 6.12 (1H, dd, J = 3.1, 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4 (CH_3), 26.9 (CH_3), 28.8 (CH_2), 42.8 (CH), 46.2 (CH), 48.7 (CH), 50.1 (CH_2), 71.4 (CH_2), 82.0 (CH), 83.1 (CH), 85.6 (CH), 105.7 (CH), 112.2 (C), 118.2 (CH_2=), 132.3 (CH=), 133.7 (CH=), 137.1 (CH=), 208.1 (CO); HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ (M+Na)$^+$, 343.1521; found 343.1525. Compound **15**: IR ν_{max} = 1707 cm^{-1}; $[\alpha]_D^{26}$ − 77.6 (c 2.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.36–1.40 (1H, m), 1.48 (3H, s), 1.82 (2H, t, J = 10.0 Hz), 2.19 (1H, td, J = 6.4, 7.6 Hz), 2.56 (1H, sextet, J = 8.6 Hz), 3.42 (1H, quintet, J = 8.7 Hz), 3.82 (1H, dd, J = 10.6, 15.0 Hz), 4.00 (1H, q, J = 9.6 Hz), 4.04 (1H, d, J = 1.7 Hz), 4.33 (1H, d, J = 2.3 Hz), 4.40 (1H, d, J = 15.0 Hz), 4.53 (1H, d, J = 3.1 Hz), 4.96 (1H, d, J = 10.3 Hz), 5.06 (1H, d, J = 17.1 Hz), 5.51 (1H, dt, J = 4.0, 10.5 Hz), 5.57 (1H, dt, J = 2, 10.5 Hz), 5.85 (1H, tdd, J = 7.2, 10.0, 18.0 Hz), 6.09 (1H, d, J = 3.2 Hz); ^{13}C NMR δ 26.5 (CH_3), 26.9 (CH_3), 35.8 (CH_2), 40.3 (CH), 41.2 (CH_2), 44.4 (CH), 51.1 (CH), 68.6 (CH_2), 84.3 (CH), 85.5 (CH), 86.3 (CH), 105.9 (CH), 112.8 (C), 113.7 (CH_2=), 125.2 (CH=), 141.6 (CH=), 141.7 (CH=), 211.8 (CO); HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ (M+Na)$^+$, 343.1521; found 343.1524. Compound **19**: IR ν_{max} = 1705 cm^{-1}; $[\alpha]_D^{25}$ − 88.4 (c 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.18 (2H, m), 1.25 (3H, s), 1.27–1.37 (1H, m), 1.39 (3H, s), 1.69 (1H, ddd, J = 3.3, 8.7, 11.7 Hz), 2.77 (1H, br s), 3.10 (1H, br s), 3.12–3.16 (1H, m), 3.72 (3H, s) 4.20 (1H, d, J = 3.6 Hz), 4.34 (1H, d, J = 11.6 Hz), 4.47 (1H, d, J = 11.6 Hz), 4.51 (1H, d, J = 3.6 Hz), 4.62 (1H, d, J = 3.6 Hz), 5.70 (1H, dd, J = 2.4, 5.4 Hz) 6.00 (1H, d, J = 3.6 Hz), 6.04 (1H, dd, J = 3.1, 5.2 Hz), 6.80 (2H, d, J = 8.5 Hz), 7.12 (2H, d, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4 (CH_3), 27.0 (CH_3), 28.6 (CH_2), 42.6 (CH), 46.2 (CH), 48.8 (CH), 50.0 (CH_2), 55.3 (OMe), 72.0 (CH_2), 81.8 (CH), 82.8 (CH), 85.4 (CH), 105.6 (CH), 112.1 (C), 113.9 (2 CH), 129.O (C), 129.7 (2 CH), 132.2 (CH=), 137.1 (CH=), 159.6 (C), 207.5 (CO); HRMS (ESI)

calcd for $C_{23}H_{28}O_6Na$ $(M + Na)^+$, 423.1783; found 423.1788. Compound **24**: mp 138–140 °C; $[\alpha]_D^{25}$ − 23.4 (*c* 1.3, $CHCl_3$); IR ν_{max} = 1719, 1724 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.32 (1H, m), 1.42 (3H, s), 1.45 (3H, s), 1.73–1.84 (1H, m), 1.95–2.02 (2H, m), 2.61 (1H, br s), 2.92 (1H, m), 3.16 (1H, m), 4.91–5.01 (3H, m), 5.36 (3H, m), 5.66–5.80 (1H, m), 5.98–5.99 (1H, m), 6.15 (1H, d, *J* = 4.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.3 (CH_3), 26.9 (CH_3), 37.1 (CH_2), 37.9 (CH_2), 43.1 (CH), 50.49 (CH), 50.52 (CH), 76.99 (CH), 83.0 (CH), 85.4 (CH), 105.6 (CH), 112.7 (C), 117.6 (CH_2=), 119.2 (CH=), 136.4 (CH=), 154.9 (CH=), 164.1 (CO), 205.1 (CO); HRMS (ESI) calcd for $C_{18}H_{22}O_6Na$ $(M+Na)^+$, 357.1314; found 357.1316.