Tetrahedron Letters 52 (2011) 2943–2945

Contents lists available at ScienceDirect

Tetrahedron Letters

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

The stereoselective total synthesis of (+)-18-(6*S*,9*R*,10*R*)-bovidic acid

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ARTICLE INFO

Article history:
Received 4 February 2011
Revised 13 March 2011
Accepted 16 March 2011
Available online 31 March 2011

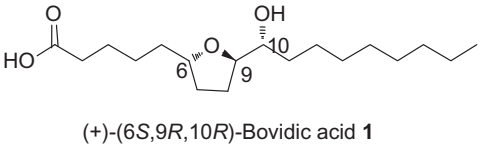
Keywords:
Bovidic acid
MacMillan α-hydroxylation
Horner–Wadsworth–Emmons reaction
Cross metathesis
Tandem dihydroxylation-S_N2 cyclization

ABSTRACT

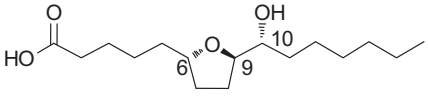
An expedient stereoselective total synthesis of 18-carbon (+)-(6*S*,9*R*,10*R*)-bovidic acid, isolated from the pelage and skin of a gaur *B. frontalis* is described using L-proline catalysed sequential α-aminoxylation and Horner–Wadsworth–Emmons olefination of aldehyde, cross metathesis and tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization reaction as the key steps.

New repellents against biting insects need to be developed to protect people from insect-transmitted diseases. The natural products present in preferred and non-preferred animal hosts of biting insects can exhibit interesting semi-chemical properties. Numerous pathogens of both man and livestock are transmitted by mosquitoes and other biting arthropods. Repellents have proven to be a reliable means of preventing biting insects.

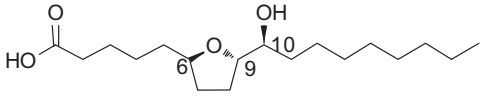
While repellents have been isolated from many naturally occurring plants and animals, recent studies by Oliver and Ishii reported identification and isolation of the natural repellent, (+)-bovidic acid **1** from the pelage and skin of a gaur *B. Frontalis*.[1,2] Decades ago, a shorter 16-carbon analogue (**3**) was isolated from sheep



(+)-(6*S*,9*R*,10*R*)-Bovidic acid **1**

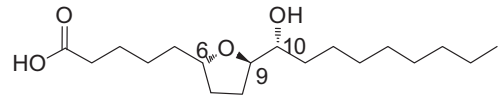


16-C-Bovidic acid **3**

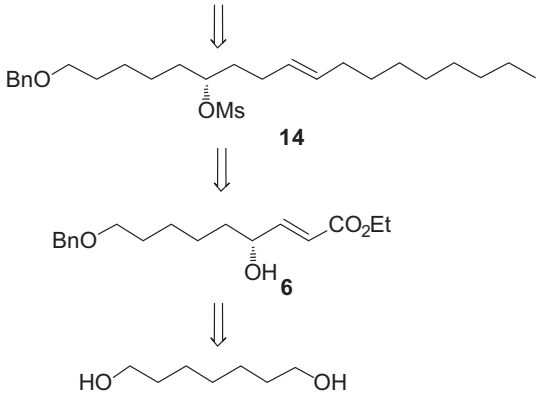


(-)-(6*R*,9*S*,10*S*)-Gaur acid **2**

Figure 1. Examples of bovidic acid and its derivatives.



(+)-(6*S*,9*R*,10*R*)-Bovidic acid **1**



Scheme 1. Retrosynthesis of (+)-bovidic acid.

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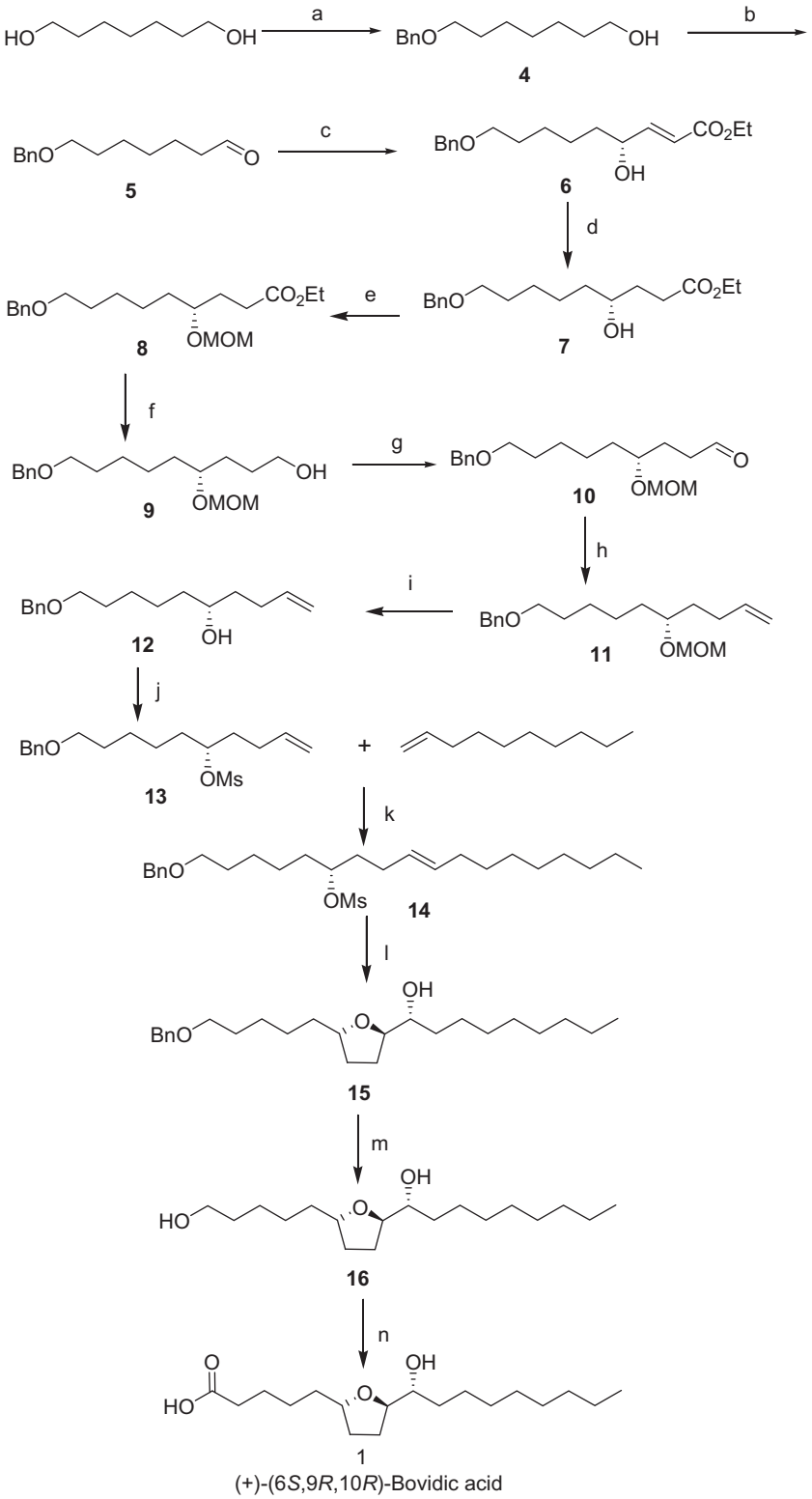
0040-4039/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.03.089

wool (Fig. 1).[3] These hydroxy furanoid fatty acids and their analogues were evaluated against *Aedes aegypti* (L) mosquitoes and the results reveal that this may generate a class of tropical repellents for use against insects that transmit pathogens to humans.[4] The (−) isomer of bovidic acid, that is, gaur acid **2** has been synthesised by Evans and co-workers.[5]



Scheme 2. Reagents and conditions: (a) (i) NaH, THF, 0–25 °C, 0.5 h; (ii) BnBr, 0–25 °C, 3 h, 90%; (b) oxalyl chloride, dry DMSO, dry DCM, −78 °C, Et_3N, 1 h, 87%; (c) nitrosobenzene (1.2 equiv), L-proline (0.4 equiv), DMSO, 20 °C, 25 min, then triethylphosphonoacetate, DBU, LiCl, 0 °C, 15 min, then MeOH, NH_4Cl, $Cu(OAc)_2$, rt, 24 h, 48% (one pot); (d) $NaBH_4$, $NiCl_2.6H_2O$, MeOH, 0 °C–rt; 3 h, 90%; (e) MOMCl, DIPEA, dry DCM, 0 °C–rt, 6 h, 94%; (f), DIBAL-H, DCM, 0 °C, 15 min, 88%; (g) oxalyl chloride, dry DMSO, dry DCM, −78 °C, Et_3N, 1 h 85%; (h) *n*-BuLi, $Ph_3P^+CH_3I^-$, THF, 0 °C–rt, over night, 85%; (i) *p*-TSA, MeOH, reflux, 30 min, 90%; (j) MsCl, Et_3N, DCM, 0 °C–rt, 4 h, 90%; (k) Grubbs II generation catalyst (3 mol %), DCM, reflux, 10 h, 75%; (l) admix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 30 h, 85%, 0 °C–rt; (m) 10% Pd/C, H_2, EtOAc, rt, 10 h, 92%; (n) TEMPO, BAIB, DCM/H_2O (1:1), 0 °C–rt, 2 h, 84%.

In continuation of our ongoing research programme on the total synthesis of biologically active molecules by desymmetrization strategy,[6] and also the inherent biological property of bovidic acid encouraged us to initiate the total synthesis of this molecule. Herein, we report a concise and flexible stereoselective synthetic route for the total synthesis of (+)-bovidic acid (**1**) starting from the readily available heptanediol by employing the MacMillan α-hydroxylation, Horner–Wadsworth–Emmons olefination, cross metathesis and tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization.

In our retrosynthetic analysis, we envisioned that the synthesis of bovidic acid could be accomplished from intermediate **14**, which can be synthesized by means of cross metathesis of compound **12** and 1-decene. The compound **12** could in turn be obtained from **6** by reduction and C1Wittig of compound **6**. This γ-hydroxy-α,β-unsaturated ester **6** can be prepared through MacMillan α-hydroxylation followed by Horner–Wadsworth–Emmons olefination of the corresponding aldehyde (Scheme 1).

Accordingly, our synthetic approach began with mono protection of 1,7-heptanediol with benzyl bromide using NaH and TBAI to give mono-benzyl ether **4** in 90% yield.[7] This monoprotected alcohol **4** was subjected to Swern oxidation to afford the corresponding aldehyde **5** in 88% yield.[8] The direct catalytic asymmetric aminoxylation of aldehyde **5** with nitrosobenzene using L-proline as a catalyst gave an intermediate α-oxyamino aldehyde with high levels of enantioselectivity[9,10] by means of α-oxidation. Subsequent olefination of aminoxy aldehyde under Horner–Wadsworth–Emmons conditions followed by the cleavage of aminoxy bond with $Cu(OAc)_2$ in MeOH at room temperature gave the γ-hydroxy-α,β-unsaturated ester **6** (96% ee, HPLC) in 48% yield.[11] The selective reduction of the double bond in γ-hydroxy-α,β-unsaturated ester **6** using $NiCl_2.6H_2O$ and $NaBH_4$[12] afforded the compound **7** in 90% yield. Thereafter, alcohol **7** was protected as its MOM ether **8** using MOMCl in the presence of the Hunig's base in dry dichloromethane. The reduction of ester **8** with DIBAL-H in DCM gave the primary alcohol **9** in 88% yield, which was further oxidized to aldehyde **10** under Swern oxidation conditions. Upon treatment of aldehyde **10** with methylene-triphenylphosphorane (generated in situ from $CH_3P^+Ph_3I^-$ and *n*-BuLi) in THF gave the olefin **11** in 85% yield. The deprotection of MOM ether was achieved by *p*-TSA in methanol to give the secondary alcohol **12** in 90% yield. The hydroxyl compound **12** was converted into its mesylate[13] **13** using $MeSO_2Cl$, Et_3N and DMAP (catalytic) in CH_2Cl_2. The mesyl ester plays a dual role as a protecting group as well as a leaving group at a later stage. Then substrate **13** was treated with 0.03 equiv of second generation Grubbs' catalyst in the presence of 4 equiv of 1-decene in dichloromethane for 10 h at reflux. The reaction proceeded smoothly and the desired cross coupled product **14** was obtained in 75% yield as *E*/*Z* isomers in 15:1 ratio.[14] A careful flash chromatography on silica gel allowed the separation of the *E* and *Z* isomers. The major *trans* isomer of cross metathesis product **14** was subjected to the Sharpless asymmetric dihydroxylation[15] using $(DHQD)_2$ PHAL, $K_3Fe(CN)_6$, K_2CO_3, and $MeSONH_2$, in *t*-BuOH/H_2O (1:1) over 30 h to afford the key tetrahydrofuran **15** in 85% yield (no traces of the other isomer was detected by ^1H NMR, since no further experiments were carried out on the enantiomerically pure compound.). Debenzylation of ether **15** with 10% Pd/C under H_2 atmosphere gave the primary alcohol **16** in good yield. Eventual oxidation of primary alcohol **16** using TEMPO and BAIB in DCM/H_2O(1:1) afforded the target acid **1** in 84% yield as a semi-solid without affecting the secondary alcohol (Scheme 2).[16] The analytical and spectral properties of the compound **1** were in good agreement with the data reported in literature.[17]

In conclusion, we have developed an efficient stereoselective route for the total synthesis of bovidic acid from a readily available 1,7-heptanediol. The salient features of this synthesis include the use of the MacMillan α-hydroxylation and HWE reaction for the construction of γ-hydroxy-α,β-unsaturated ester in a single step, Grubbs cross metathesis and tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization, which allow the preparation of a target molecule in a short and flexible route.

Acknowledgements

K.R. thanks CSIR, New Delhi and U.V.S.R. thanks UGC, New Delhi, for the award of fellowships.

References and notes

1. Oliver, J. E.; Weldon, P. J.; Peterson, K. S.; Schmidt, W. F.; Debboun, M. Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, USA, March 23-27, **2003**.
2. Hideki, I.; Sonja, K.; Yasuhiro, I.; Nina, B.; Koji, N.; Paul, J. W. *J. Nat. Prod.* **2004**, *67*, 1426.
3. Ito, S.; Endo, K.; Inoue, S.; Nozoe, T. *Tetrahedron Lett.* **1971**, *12*, 4011.
4. Tran, K.; Chauhan, K. R. *Biopestic. Int.* **2007**, *3*, 53.
5. Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uraguchi, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4788.
6. For recent publications see: (a) Yadav, J. S.; Satheesh, G.; Murthy, C. V. S. R. *Org. Lett.* **2010**, *12*, 2544; (b) Yadav, J. S.; Rajender, V.; Gangadhar, Y. *Org. Lett.* **2010**, *12*, 348; (c) Yadav, J. S.; Mohapatra, D. K.; Hossain, S. S.; Dhara, S. *Tetrahedron Lett.* **2010**, *51*, 3079; (d) Yadav, J. S.; Narasimhulu, G.; Reddy, N. M.; Reddy, B. V. S. *Tetrahedron Lett.* **2010**, *51*, 1574.
7. Jun, I. S.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Kimoon, K. *Tetrahedron Lett.* **2000**, *41*, 471.
8. Corey, E. J.; Marafat, A.; Laguzza, B. C. *Tetrahedron Lett.* **1981**, *22*, 3339.
9. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am Chem. Soc.* **2003**, *125*, 10808.
10. For other reports on proline-catalyzed oxidation of aldehydes see: (a) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem.* **2009**, *74*, 9531; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (d) Chandrasekhar, S.; Yaragorla, S. R.; Sreelakshmi, L. *Tetrahedron Lett.* **2007**, *48*, 7339; (e) Zhong, G. *Chem. Commun.* **2004**, 606.
11. (a) Yadav, J. S.; Reddy, U. V. S.; Anusha, B.; Reddy, B. V. S. *Tetrahedron Lett.* **2010**, *51*, 5529; (b) Sabitha, G.; Chandrashekhar, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 3824; (c) Yadav, J. S.; Reddy, U. V. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 5984; (d) Zhong, G.; Yu, Y. *Org. Lett.* **2004**, *6*, 1637; (e) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696; (f) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461.
12. Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.
13. Marshal, J. A.; Sabatini, J. J. *Org. Lett.* **2005**, *7*, 4819.
14. Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Germany, 2003; (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360; (d) Tetsuya, Y.; Hiroko, H.; Toshikazu, H.; Shigeo, K. *Org. Lett.* **2006**, *8*, 5569.
15. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768; (b) Kolb, H. C.; Van-Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (c) Mohapatra, D. K.; Pavankumar, D.; Hasibur, R.; Pal, R. *Tetrahedron Lett.* **2009**, *50*, 6276.
16. (a) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293; (b) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
17. *Spectral data for compound* **6**: Light yellow liquid, $[\alpha]_D^{25}$ +3 (*c* 0.75, $CHCl_3$); IR (neat): υ_{max} 3430, 2922, 2852, 1717, 1655, 1641, 1262, 1096, 803, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.21 (m, 5H), 6.87 (dd, 1H, *J* = 4.5, 15.8 Hz), 5.96 (dd, 1H, *J* = 1.5, 15.1 Hz), 4.4 (s, 2H), 4.21–4.11 (m, 3H), 3.42 (t, 2H, *J* = 6.0 Hz), 1.61–1.24 (m, 11H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 150.0, 138.5, 128.3, 127.6, 127.4, 120.1, 72.8, 70.9, 70.1, 60.4, 36.5, 29.5, 26.0, 24.9, 14.2; ESI-MS: *m*/*z*: 307 $(M+H)^+$, 324 $(M+NH_4)^+$, 329 $(M+Na)^+$; Compound **15**: Colourless liquid, $[\alpha]_D^{25}$ +8.4 (*c* 0.4, $CHCl_3$); IR (neat): υ_{max} 3449, 2922, 2852, 1637, 1461, 1098, 726 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.27 (m, 5H), 4.46 (s, 2H), 3.89-3.81 (m, 1H), 3.72 (q, 1H, *J* = 7.5 Hz), 3.46–3.40 (m, 2H), 3.34–3.26 (m, 1H), 2.26–2.22 (m, 1H), 2.04–1.89 (m, 2H), 1.63–1.23 (m, 24H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.3, 127.6, 127.4, 81.9, 79.1, 74.1, 72.8, 70.3, 35.6, 33.4, 32.5, 31.9, 30.2, 29.8, 29.6, 29.3, 28.4, 26.3, 26.1, 25.7, 22.7, 14.2; ESI-MS: *m*/*z*: 390 $(M)^+$, 391 $(M+H)^+$; Compound **1**: Colourless semi solid, $[\alpha]_D^{25}$ +7.3 (*c* 0.2, $CHCl_3$); IR (neat): υ_{max} 3447, 2921, 2852, 1716, 1461, 1260, 1081, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.93–3.83 (m, 1H), 3.74 (q, 1H, *J* = 7.5 Hz), 3.36–3.28 (m, 1H), 2.34 (t, 2H, *J* = 7.5 Hz), 2.09–1.90 (m, 2H), 1.69–1.32 (m, 12 H), 1.27 (s, 12H), 0.88 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 82.1, 78.9, 74.0, 35.3, 33.9, 33.5, 32.7, 32.1, 29.9, 29.8, 29.5, 28.6, 25.8, 25.7, 24.8, 22.9, 14.3; ESI-MS: *m*/*z*: 315 $(M+H)^+$, 337 $(M+Na)^+$.