Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 9357–9360

A facile route for the synthesis of limonidilactone analogues from andrographolide☆

Siva Sanjeeva Rao Thunuguntla, Vijay Kumar Nyavanandi and Srinivas Nanduri*

Discovery Chemistry, Discovery Research, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, India

Received 2 August 2004; revised 12 October 2004; accepted 22 October 2004

Abstract—Labdane diterpenes are an important class of natural products with a wide variety of biological properties. (−)-Limonidilactone is a labdane diterpene with a novel skeleton isolated from *Vitex limonifolia*. A new semi-synthetic route from andrographolide, the major constituent of *Andrographis paniculata*, has been described towards the synthesis of novel labdanes having a limonidilactone type skeleton.

Labdane diterpenes are a widely distributed class of biologically active natural products isolated from higher plants.[1] Compounds in this class, for example, polygodiol,[2] warburganal,[3] coronarin A[4] and galanolactone,[5] have attracted special attention due to their significant antifeedant, antitumour and antifungal activities. Generation of compound libraries having the main skeletal core of these biologically active molecules constitutes an important aspect of drug discovery aimed at synthesizing more potent and novel compounds. The structural complexity of these molecules and often, their low natural abundance pose a challenge to library generation. Semi-synthetic transformations performed on the abundantly available natural products can be used to achieve this objective.[6]

(−)-Limonidilactone **1a**, a labdane diterpene was isolated from *Vitex limonifolia* by Suksamrarn and coworkers.[7] The synthesis of (+)-limonidilactone **1b** from zamoranic acid has been reported.[8] In continuation of our studies towards the generation of structurally diverse labdane diterpenes from andrographolide **2**,[9] we planned to synthesize compounds **3** and **4** possessing the skeletal core of limonidilactone. Compounds **3** and **4** possess additional oxygen substituents on the decalin system. These oxygen substituents could be used as diversity points to generate more limonidilactone analogues. The synthesis of **3** and **4** has been achieved through a key intermediate **5**, which in turn was prepared from andrographolide as shown in Figure 1.

The hydroxyls at C-3 and C-19 on andrographolide were first protected as an acetonide to afford **6**. Treatment of **6**, with a catalytic amount of pyridinium dichromate (0.05 mol equiv) led to the rearrangement of the allylic hydroxyl at C-14 to give compound **7**, 3-[1-hydroxy-2-(3,3,6a,10b-tetramethyl-8-methylene-decahydronaphtho[2,1-*d*][1,3]dioxin-7-yl)-ethyl]-5*H*-furan-2-one. Protection of the C-12 hydroxyl as the *t*-butyldimethylsilyl ether and subsequent removal of the isopropylidene moiety gave the key intermediate **5** (Scheme 1).

Compound **3** was synthesized as shown in Scheme 2. Acetylation of the hydroxyls at C-3 and C-19 in **5** led to **9**. Allylic hydroxylation[10] of **9** using selenium dioxide gave **10**. Rearrangement of the C-7 allylic hydroxyl in **10** was achieved by preparing the C-7 mesylate and subsequent treatment with sodium acetate.[10] Under these conditions, the TBDMS-ether at C-12 was also hydrolyzed leading to the corresponding C-12 hydroxy compound **11**. Oxidative cyclization[11] of the C-17 and C-12 hydroxyls led to the formation of **3**.[12]

The synthesis of compound **4**, was achieved as shown in Scheme 3. The lactone group in compound **5** was reduced with DIBAL-H to give furanolabdane **12**. Acetylation of the C-3 and C-19 hydroxyls gave **13**.

☆ DRL publication no. 438.

* Corresponding author. Tel.: +91 40 23045439; fax: +91 40 23045438; e-mail: nandurisrinivas@drreddys.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.135

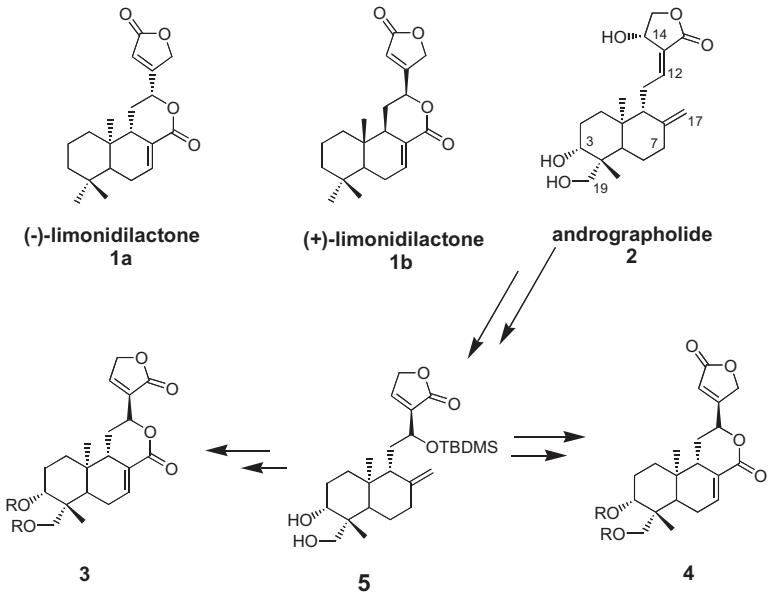
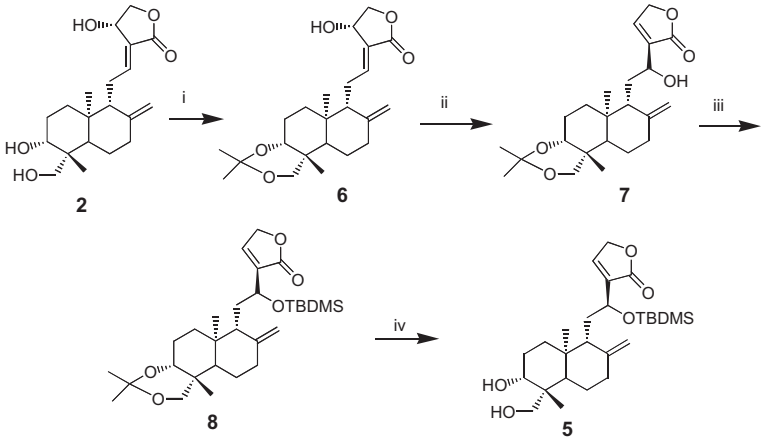
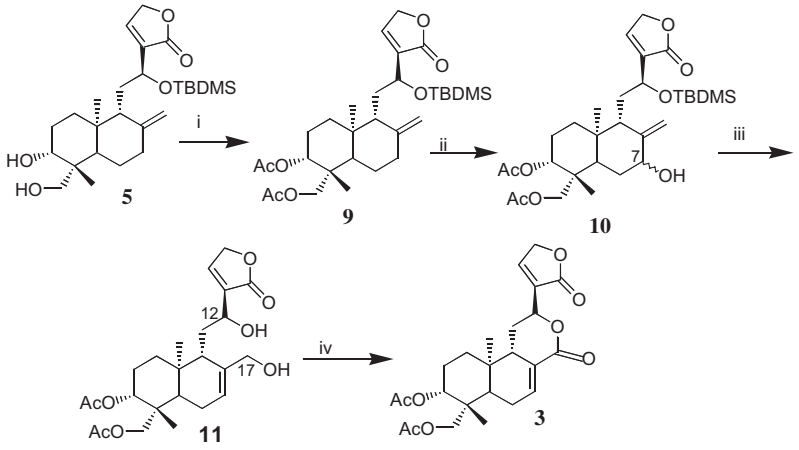


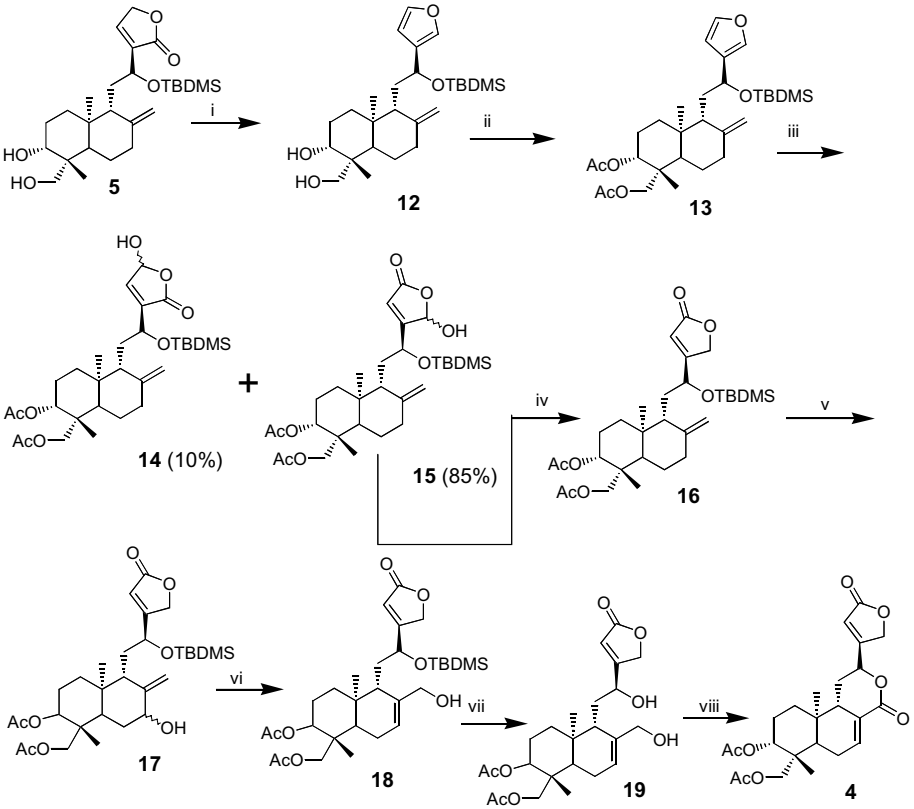
Figure 1.



Scheme 1. Reagents and conditions: (i) 2,2-dimethoxypropane/PPTS/DMSO/benzene/reflux/2 h (95%); (ii) PDC/DCM/rt/5 h (80%); TBDMS-Cl/imidazole/DMF/rt/8 h (85%); (iv) AcOH/H_2O/rt/15 min (90%).



Scheme 2. Reagents and conditions: (i) Ac_2O/py/rt/6 h (95%); (ii) SeO_2/TBHP/DCM/rt/48 h (60%); (iii) (a) Ms-Cl/py/DCM/rt/1 h (85%); (b) NaOAc/acetone/water/reflux/2 h (50%); (iv) iodobenzene diacetate/TEMPO/DCM/rt/1 h (80%).



Scheme 3. Reagents and conditions: (i) 20% DIBAL-H in toluene/−78 °C/2 h/(50%); (ii) Ac_2O/py/rt/2 h (95%); (iii) hν/O_2/DIEA/rose bengal; (iv) $NaBH_4$/THF/0 °C/2 h (75%); (v) SeO_2/TBHP/DCM/rt/48 h (50%); (vi) (a) Ms-Cl/py/DCM/rt/1 h (85%); (b) NaOAc/acetone/water/reflux/2 h (55%); (vii) AcOH/H_2O (7:3)/rt/24 h (75%); (viii) iodobenzene diacetate/TEMPO/DCM/rt/1 h (85%).

Photochemical oxidation[13] of the furan moiety in **13** gave a mixture of γ-hydroxy butenolides **14** and **15**, which were separated by column chromatography. Compound **15**, was further reduced with sodium borohydride to give **16**. Subsequently, allylic hydroxylation at C-7 followed by allylic rearrangement of the C-7 hydroxyl group gave compound **18**. However, the C-12-TBDMS ether was not hydrolyzed under these conditions. Hence, deprotection was carried out with aq acetic acid to yield **19**. Oxidative cyclization of **19** was carried out as before to give compound **4**.[14]

The stereochemistry of **3** and **4** at C-12 was assigned based on spectral analysis in comparison with the reported values of **1a** and **1b**.[8]

In conclusion, we have successfully converted andrographolide, the abundantly available natural product, into compounds **3** and **4**, which could be further utilized for making a number of further limonidilactone analogues.

Acknowledgements

The authors would like to thank Professor Javed Iqbal, Dr. R. Rajagopalan and Dr. A. Venkateswarlu for their constant encouragement and the Analytical Department for spectral support.

References and notes

1. (a) Mann, J.; Davision, R. S.; Hobbs, J. B.; Banthorpe, D. V.; Harbone, J. B. *Natural Products: Their Chemistry and Biological Significance*; Longman Group Ltd: New York, 1994; (b) Hanson, J. R. *Nat. Prod. Rep.* **2001**, *18*, 88.
2. Jansen, B. J. M.; de Groot, A. *Nat. Prod. Rep.* **1991**, *8*, 319.
3. Razmilic, I.; Sierra, J.; Lopez, J.; Cortes, M. *Chem. Lett.* **1985**, 1113.
4. Itokawa, H.; Morita, H.; Katou, I.; Takeya, K.; Cavalheiro, A. J.; de Oliveira, R. C. B.; Ishege, M.; Motidome, M. *Planta Med.* **1988**, 311.
5. Morita, H.; Itokawa, H. *Planta Med.* **1988**, 117.
6. Biabani, M. A. F.; Grover, R. K.; Singh, S. K.; Kumar, S.; Raj, K.; Roy, R.; Kundu, B. *Tetrahedron Lett.* **2001**, *42*, 7119.
7. Aphaijitt, S.; Nimgirawath, K.; Suksamrarn, A.; Tooptakong, U. *Aust. J. Chem.* **1995**, *48*, 133.
8. Marcos, I. S.; Moro, R. F.; Carballares, S.; Urones, J. G. *Tetrahedron* **2001**, *57*, 713.
9. Srinivas, N.; Vijay, K. N.; Siva, S. R. T.; Mahendar, V.; Sridevi, K.; Sriram, R.; Javed, I. *Tetrahedron Lett.* **2004**, *45*, 4883.
10. Barrero, A. F.; Alvarez-Manzaneda, E.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron Lett.* **1994**, *35*, 2945.
11. Hansen, M. T.; Gordon, J. F.; Priscilla, L.; Jiehao, C.; Jason, N. A.; Craig, J. F. *Tetrahedron Lett.* **2003**, *57*, 57.
12. Spectral data for compound **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (t, 1H, H-14), 7.37 (m, 1H, H-7), 5.1 (dd, J = 9.6, 1.6 Hz, 1H, H-12), 4.87 (m, 2H, H-15), 4.63 (dd, J = 4.4, 4.4 Hz, 1H, H-3), 4.42 (d, J = 11.6 Hz,

1H, H-19a), 4.26 (d, $J = 11.6$ Hz, 1H, H-19b), 2.55–2.35 (m, 3H), 2.07 (s, 3H, O-acetyl), 2.06 (s, 3H, O-acetyl), 1.90–1.35 (m, 7H), 1.04 (s, 3H, H-18), 0.80 (s, 3H, H-20); CIMS: 447 (100%, $M^+ + 1$), 387 ($M^+ + 1 - AcOH$), 327 ($M^+ + 1 - 2AcOH$).

13. Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A.; Mueller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171.
14. Spectral data for compound **4**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 1H, H-7), 6.10 (m, 1H, H-14), 5.24 (d, $J = 11.2$ Hz, 1H, H-12), 4.96 (s, 2H, H-16), 4.62 (dd, $J = 4.8, 4.8$ Hz, 1H, H-3), 4.44 (d, $J = 11.6$ Hz, 1H, H-19a), 4.26 (d, $J = 11.6$ Hz, 1H, H-19b), 2.55–2.35 (m, 3H), 2.08 (s, 3H, O-acetyl), 2.07 (s, 3H, O-acetyl), 1.95–1.25 (m, 7H), 1.04 (s, 3H, H-18), 0.84 (s, 3H, H-20). CIMS: 447 (100%, $M^+ + 1$), 387 ($M^+ + 1 - AcOH$), 327 ($M^+ + 1 - 2AcOH$).