Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1563–1565
Tetrahedron Letters

Semi-synthesis of secologanin analogues

M. Carmen Galan and Sarah E. O'Connor*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA

Received 12 December 2005; accepted 3 January 2006

Abstract—Secologanin, a complex iridoid terpene natural product, was derivatized at the vinyl and ester functional groups using cross-metathesis and transesterification methodology, respectively.

Terpene indole alkaloids are derived from the terpene iridoid glycoside secologanin (**1**) (Fig. 1). Secologanin is a densely functionalized molecule containing one free and two masked aldehyde groups, along with a vinyl and ester moiety and a glycosidic linkage.[1] In the first step of terpene indole alkaloid biosynthesis, strictosidine synthase catalyzes a Pictet–Spengler condensation between secologanin and tryptamine.[2,3] The glucose is next hydrolyzed, and the resulting hemiacetal, previously masked by the glycosidic linkage, triggers the rearrangement of the molecule.[4,5] Secologanin therefore plays a key role in generating the complex structure of terpene indole alkaloids and it has been previously used as an enantiomeric template to chemically synthesize alkaloid natural products.[6,7]

Here we report in detail the semi-synthesis of a series of secologanin analogues, in which two of the key functional groups of secologanin have been modified (Fig. 1). These analogues will be used to evaluate the substrate requirements of the terpene indole alkaloid biosynthetic pathway, and potentially, will be used in the enzymatic synthesis of terpene indole alkaloid derivatives. Secologanin was obtained by an optimized multigram-scale isolation protocol from a local source of *Lonicera tatarica*.[8]

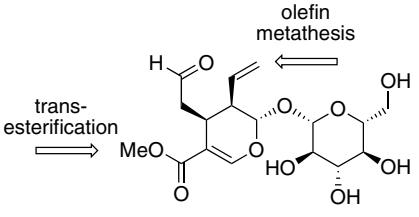


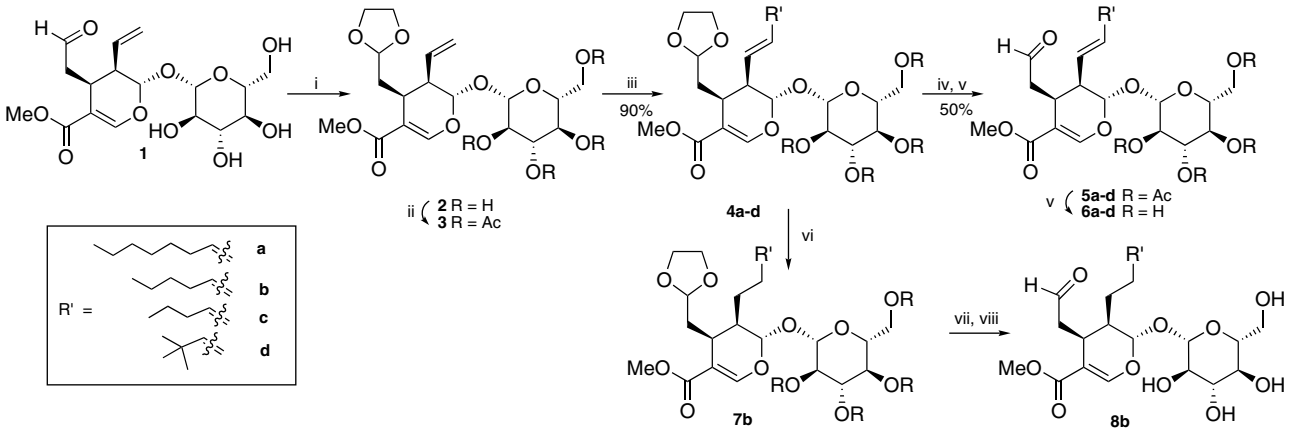
Figure 1. Derivatization of secologanin **1**.

Olefin cross metathesis (CM) was used to introduce a variety of alkyl groups at the vinyl position of secologanin (i.e., compounds **6a–d**, Scheme 1). Although we hoped to use unprotected secologanin directly, attempts to incorporate alkyl groups onto the vinyl functionality of the unprotected molecule failed, most likely due to the insolubility of secologanin in solvents used for olefin CM. Following reported procedures, the glycan was peracetylated and the aldehyde protected as an acetal to provide the 'protected' secologanin, compound **3**.[9] Reactions of **3** with Grubbs catalyst second generation (5 mol %) in the presence of a range of alkenes of different lengths (**a–d**) afforded compounds **4a–d** in good yield (**4a** 90%, **4b** 92%, **4c** 97%, and **4d** 90%; Scheme 1).[10] In every case, we observed (>95%) the E stereoisomer. After derivatization at the vinyl position, the products were deprotected in a two-step procedure: the acetal was first hydrolyzed by treatment with 0.2 M hydrochloric acid in THF, and the acetates were subsequently removed under mild basic conditions to afford compounds **6a–d**[11] in yields of approximately 50% (two steps). Alternatively, compound **4b** was subjected to catalytic hydrogenation to reduce the alkene (**7b**), and was then deprotected to yield a reduced secologanin derivative **8b**.[12]

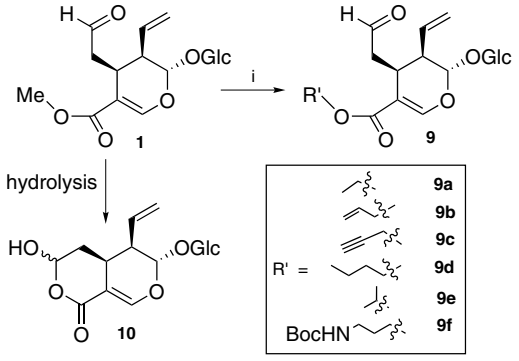
A series of ester derivatives were obtained by transesterification[13] of secologanin (compounds **9a–f**, Scheme 2). Derivatization of the ester moiety of secologanin is

* Corresponding author. Tel.: +1 617 324 0180; fax: +1 617 324 0505; e-mail: soc@mit.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.009



Scheme 1. Cross metathesis reaction of secologanin with terminal olefins and subsequent deprotection. Reagents and conditions: (i) $HOCH_2CH_2OH$, Dowex 50WX2 H^+; (ii) Ac_2O, Pyridine; (iii) Grubbs II (10 mol %), alkene, toluene, 100 °C; (iv) HCl aq (1 M); (v) K_2CO_3, MeOH; (vi) H_2, Pd/C, MeOH; (vii) HCl aq (1 M); (viii) K_2CO_3, MeOH.



Scheme 2. Transesterification on secologanin **1**. Reagents and conditions: (i) $NaHCO_3$, R′OH, Δ. Hydrolysis of the ester under acidic conditions results in the formation of a hemiacetal **10**.

complicated by the fact that after hydrolysis of the ester, a cyclic hemiacetal can form (Scheme 2).[14] Secologanin was dissolved in a variety of alcohols in the presence of $NaHCO_3$, and kept at 90 °C or refluxed for 3 h (Scheme 2). Under these mild conditions, the ethyl (**9a**, 65%), allyl (**9b**, 57%), propargyl (**9c**, 84%), butyl (**9d**, 93%), and isopropyl (**9e**, 45%) ester derivatives of unprotected secologanin were obtained. In the same manner, a *tert*-butyl *N*-(3-hydroxypropyl)carbamate linker was introduced (**9f**, 62%). This general trans-esterification method will be used to introduce a variety of functional groups or chemical tags on secologanin.[15]

Qualitative studies evaluated the enzymatic activity of a few of these unnatural secologanin derivatives with strictosidine synthase and strictosidine glucosidase.[8] Briefly, while bulkier groups at the vinyl position completely prevented turnover (compounds **6b**,**d**), transesterification at the methyl ester with larger alkyl groups (compounds **9a**,**b**) yielded substrates that were turned over by the enzyme to yield the corresponding strictosidine analogues, suggesting that this is a promising position for derivatization for enzymatic biosynthesis studies.

Acknowledgements

We gratefully acknowledge financial support from the Smith Family Medical Foundation, the American Chemical Society Petroleum Research Fund (41727-G4), 3M, Amgen Inc., and MIT.

References and notes

1. Tietze, L. F. *Angew. Chem.* **1983**, *95*, 840–853.
2. Lee, S. L.; Hirata, T.; Scott, A. I. *Tetrahedron Lett.* **1979**, *8*, 691–694.
3. Treimer, J. F.; Zenk, M. H. *Eur. J. Biochem.* **1979**, *101*, 225–233.
4. Geerlings, A.; Ibanez, M. M.-L.; Memelink, J.; Van der Heijden, R.; Verpoorte, R. *J. Biol. Chem.* **2000**, *275*, 3051–3056.
5. Gerasimenko, I.; Sheludko, Y.; Ma, X.; Stockigt, J. *Eur. J. Biochem.* **2002**, *269*, 2204–2213.
6. Brown, R. T.; Curless, D. *Tetrahedron Lett.* **1986**, *27*, 6005–6008.
7. Brown, R. T.; Jones, M. F. *J. Chem. Soc., Chem. Commun.* **1986**, 699–700.
8. McCoy, E.; Galan, M. C.; O'Connor, S. E. submitted for publication.
9. Tietze, L. F.; Henke, S.; Remberg, G. *Liebigs Ann. Chem.* **1986**, 1413–1427.
10. Based on recovered starting material. Typical yields of recovered starting material for these reactions was 50%.
11. Characterization of compounds **6a**–**d** (hydrated aldehyde observed in 1D NMR spectra): Compound **6a**: ^1H NMR (CD_3OD, 500 MHz): 7.43 (d, 1H, $J = 2$ Hz), 5.77–5.66 (m, 1H), 5.49–5.42 (m, 1H), 5.29 (dd, 1H, $J = 9.5$, 15.3 Hz), 4.93 (m, 1H), 4.67 (dd, 1H, $J =< 1$, 8.0 Hz), 4.51 (dd, 1H, $J = 4.3$, 7.3 Hz), 3.98–3.86 (m, 2H), 3.84–3.78 (m, 1H), 3.70 (s, 3H), 3.74–3.64 (m, 1H), 3.21 (t, 1H, $J = 7.9$ Hz), 3.04–2.85 (m, 1H), 2.76–2.61 (m, 1H), 2.20–2.03 (m, 2H), 1.80–1.74 (m, 1H), 1.64–1.56 (m, 1H), 1.46–1.24 (m, 8H), 0.97–0.84 (m, 3H). ESI ($C_{23}H_{36}NaO_{10}$): *m/z* 495.4 $[M+Na]^+$. Compound **6b**: ^1H NMR (CD_3OD, 500 MHz): 7.43 (d, 1H, $J = 2$ Hz), 5.77–5.65 (m, 1H), 5.50–5.43 (m, 1H), 5.30 (dd, 1H, $J = 9.2$, 15.3 Hz), 4.95 (m, 1H), 4.67 (dd, 1H, $J =< 1$, 8.0 Hz), 4.51 (dd, 1H, $J = 4.3$, 7.3 Hz), 3.98–3.86 (m, 2H), 3.85–3.78 (m, 1H), 3.70 (s, 3H), 3.74–3.64 (m, 1H), 3.20 (t, 1H, $J = 8.0$ Hz),

3.03–2.85 (m, 1H), 2.76–2.61 (m, 1H), 2.17–2.03 (m, 2H), 1.80–1.72 (m, 1H), 1.64–1.56 (m, 1H), 1.46–1.28 (m, 4H), 0.98–0.85 (m, 3H). ESI ($C_{21}H_{32}NaO_{10}$): *m/z* 467.5 $[M+Na]^+$. Compound **6c**: ^1H NMR (CD_3OD, 500 MHz): 7.42 (d, 1H, $J = 2$ Hz), 5.77–5.65 (m, 1H), 5.45 (dd, 1H, $J = 4.9$, 9.5 Hz), 5.30 (dd, 1H, $J = 8.9$, 15.3 Hz), 4.94 (dd, 1H, $J = 4.3$, 10.1 Hz), 4.67 (dd, 1H, $J = 1.22$, 7.3 Hz), 4.51 (dd, 1H, $J = 4.3$, 7.3 Hz), 3.98–3.86 (m, 2H), 3.84–3.78 (m, 1H), 3.70 (s, 3H), 3.73–3.64 (m, 1H), 3.20 (m, 1H), 3.03–2.84 (m, 1H), 2.76–2.62 (m, 1H), 2.18–2.01 (m, 2H), 1.80–1.71 (m, 1H), 1.64–1.56 (m, 1H), 1.48–1.38 (m, 2H), 1.0–0.88 (m, 3H). ESI ($C_{20}H_{30}NaO_{10}$): *m/z* 453.1 $[M+Na]^+$. Compound **6d**: ^1H NMR (CD_3OD, 500 MHz): 7.43 (d, 1H, $J = 2$ Hz), 5.77–5.65 (m, 1H), 5.49–5.41 (m, 1H), 5.36–5.18 (m, 1H), 4.97 (m, 1H), 4.68 (m, 1H), 4.51 (dd, 1H, $J = 4.3$, 7.3 Hz), 3.98–3.86 (m, 2H), 3.85–3.78 (m, 1H), 3.70 (s, 3H), 3.76–3.63 (m, 1H), 3.20 (t, 1H, $J = 7.5$ Hz), 3.03–2.85 (m, 1H), 2.76–2.60 (m, 1H), 2.17–2.03 (m, 2H), 1.04 (s, 9H). ESI ($C_{21}H_{32}NaO_{10}$): *m/z* 467.5 $[M+Na]^+$.

12. Characterization of compound **8b** (hydrated aldehyde observed in 1D NMR spectra): ^1H NMR (CD_3OD, 500 MHz): 7.46 (d, 1H, $J = 2$ Hz), 5.48–5.39 (m, 1H), 4.86 (m, 1H), 4.72 (dd, 1H, $J = 3.1$, 7.8 Hz), 4.54 (d, 1H, $J = 7.9$ Hz), 4.42 (t, 1H, $J = 5.4$ Hz), 4.13–4.04 (m, 1H), 3.98–3.86 (m, 2H), 3.84–3.76 (m, 1H), 3.70 (s, 3H), 3.74–3.62 (m, 1H), 3.20 (t, 1H, $J = 9.2$ Hz), 2.90–2.85 (m, 1H), 2.76–2.62 (m, 1H), 1.90–1.72 (m, 2H), 1.66–1.52 (m, 2H), 1.46–1.22 (m, 6H), 0.98–0.85 (m, 3H). ESI ($C_{21}H_{34}NaO_{10}$): *m/z* $[M+Na]^+$ 469.3.
13. For a review on transesterification see: Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470.
14. Tomassini, L.; Cometa, M. F.; Serafini, M.; Nicoletti, M. *J. Nat. Prod.* **1995**, *11*, 1756–1758.
15. Characterization of Compounds **9a**–**f**: Compound **9a**: ^1H NMR (CD_3OD, 500 MHz): 9.74 (s, 1H), 7.43 (s, 1H), 5.79–5.70 (m, 1H), 5.60–5.48 (m, 1H), 5.44 (dd, 1H, $J = 2.5$, 9.8 Hz), 5.36–5.22 (m, 1H), 4.68 (d, 1H, $J = 7.9$ Hz), 4.68–4.58 (m, 1H), 4.20–4.12 (m, 1H), 4.06–3.98 (m, 1H), 3.92–3.86 (m, 2H), 3.74–3.63 (m, 1H), 3.40–3.10 (m, 1H), 2.74–2.64 (m, 1H), 2.10 (dd, 1H, $J = 6.7$, 2.8 Hz), 1.98 (dd, 1H, $J = 4.0$, 2.5 Hz), 1.50 (dd, 2H, $J = 9.8$, 13.4 Hz), 1.34–1.20 (m, 3H). ESI ($C_{18}H_{26}NaO_{10}$): *m/z* 425.5 $[M+Na]^+$. Compound **9b**: ^1H NMR (CD_3OD, 500 MHz): 9.66 (s, 1H), 7.46 (s, 1H), 6.01–5.80 (m, 1H), 5.78–5.67 (m, 1H), 5.63–5.44 (m, 2H), 5.38–5.14 (m, 3H), 4.67 (d, 1H, $J = 7.8$ Hz), 4.74–4.53 (m, 2H), 4.39–4.28 (m, 1H), 4.24–4.13 (m, 2H), 3.89 (d, 1H, $J = 9.9$ Hz), 3.71–3.61 (m, 1H), 3.20–3.10 (m, 2H), 2.76–2.60 (m, 1H), 1.98–1.83 (m, 1H), 1.80–1.65 (m, 1H). ESI ($C_{19}H_{26}NaO_{10}$): *m/z* 437.1 $[M+Na]^+$. Compound **9c**: ^1H NMR (CD_3OD, 500 MHz): 9.60 (s, 1H), 7.62 (s, 1H), 5.70–5.62 (m, 1H), 5.61–5.48 (m, 1H), 5.38–5.27 (m, 1H), 4.69 (t, 2H, $J = 7.9$ Hz), 4.47 (t, 1H, $J = 2.44$ Hz), 4.40 (d, 1H, $J =< 2$ Hz), 3.91 (dd, 1H, $J =< 2$, 11.9 Hz), 3.71–3.63 (m, 1H), 3.44–3.24 (m, 2H), 3.24–3.16 (m, 1H), 2.98–2.94 (m, 1H), 2.68 (dd, 1H, $J = 5.8$, 9.8 Hz), 2.06–1.98 (m, 1H), 1.93–1.85 (m, 1H), 1.83–1.74 (m, 1H), 1.58–1.46 (ddd, 1H, $J = 10.1$, 9.8, 13.43 Hz). ESI ($C_{19}H_{24}NaO_{10}$): *m/z* 435.1 $[M+Na]^+$. Compound **9d**: ^1H NMR (CD_3OD, 500 MHz): 9.59 (s, 1H), 7.60 (s, 1H), 5.80–5.70 (m, 1H), 5.61–5.48 (m, 1H), 5.37–5.22 (m, 1H), 4.69 (t, 2H, $J = 7.9$ Hz), 4.67–4.58 (m, 1H), 4.16–4.08 (m, 1H), 4.01–3.94 (m, 1H), 3.91 (dd, 1H, $J =< 2$, 11.9 Hz), 3.71–3.64 (m, 1H), 3.64–3.58 (m, 1H), 3.45–3.24 (m, 2H), 3.24–3.15 (m, 1H), 3.02–2.94 (m, 1H), 2.68 (m, 1H), 2.10–1.92 (m, 1H), 1.78–1.56 (m, 2H), 1.52–1.38 (m, 2H), 1.02–0.90 (m, 3H). ESI ($C_{20}H_{30}NaO_{10}$): *m/z* 453.1 $[M+Na]^+$. Compound **9e**: ^1H NMR (CD_3OD, 500 MHz): 9.67 (s, 1H), 7.43 (s, 1H), 5.80–5.68 (m, 1H), 5.63–5.46 (m, 1H), 5.38–5.20 (m, 3H), 4.66 (dd, 1H, $J = 2.3$, 7.9 Hz), 4.72–4.58 (m, 1H), 3.90 (d, 1H, $J = 11.9$ Hz), 3.71–3.61 (m, 2H), 3.24–3.10 (m, 3H), 2.76–2.60 (m, 1H), 2.20–1.88 (m, 1H), 1.78–1.58 (m, 1H), 1.29 (s, 6H). ESI ($C_{19}H_{28}NaO_{10}$): *m/z* 439.2 $[M+Na]^+$. Compound **9f**: ^1H NMR (CD_3OD, 500 MHz): 9.72 (s, 1H), 7.64 (s, 1H), 5.80–5.70 (m, 1H), 5.69–5.48 (m, 1H), 5.42 (dd, 1H, $J = 2.1$, 9.8 Hz),5.38–5.12 (m, 3H), 4.72–4.60 (m, 1H), 4.68 (d, 1H, $J = 7.6$ Hz), 4.13 (m, 1H), 4 (m, 1H), 3.91 (d, 1H, $J = 11.9$ Hz), 3.72–3.60 (m, 1H), 3.24 (m, 2H), 3.41–3.26 (m, 4H), 2.71 (m, 2H), 2.02 (d, 1H, $J = 12.5$ Hz), 0.99 (t, 9H, $J = 6.7$ Hz). ESI ($C_{24}H_{37}NaO_{12}$): *m/z* 554.2 $[M+Na]^+$.