ORGANIC LETTERS

2000
Vol. 2, No. 18
2893−2895

Efficient One-Step Conversion of Primary Aliphatic Amines into Primary Alcohols: Application to a Model Study for the Total Synthesis of (±)-Scopadulin

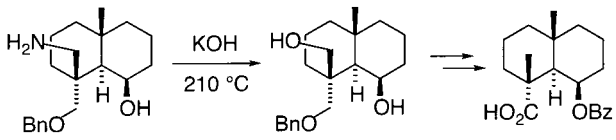
S. M. Abdur Rahman, Hiroaki Ohno, Naoyoshi Maezaki, Chuzo Iwata, and Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

t-tanaka@phs.osaka-u.ac.jp

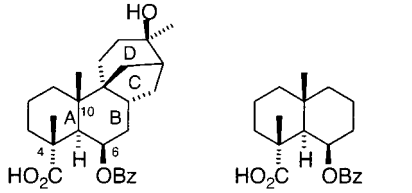
Received July 14, 2000

ABSTRACT



Treatment of primary aliphatic amines with KOH in diethylene glycol at 210 °C gives primary alcohols directly in good yields. A synthetic application to a model study of (±)-scopadulin is also described.

Scopadulin **1**, a tetracyclic diterpenoid, was isolated from the Paraguan plant *Scoparia dulcis* (fam. Scrophulariaceae) in 1990, as the first aphidicolane diterpenoid from higher plants. The structure and the stereochemistry of scopadulin were determined by T. Hayashi and co-workers.[1] Its structural complexity, due to the presence of three quaternary carbons and eight stereocenters, along with its notable antiviral and cytotoxic activities attracted synthetic chemists as a worthy challenge. However, no synthetic pathway to scopadulin has been reported to date.[2] Although we have established the construction of a similar C/D ring system in the successful synthetic study of aphidicolin,[3] the progress of a synthetic study of scopadulin was hampered due to several failed attempts to construct the A/B ring system with the desired functionalities. Accordingly, we turned our attention to the synthesis of model compound **2** bearing the requisite functionalities and stereochemical configuration prior to the total synthesis of scopadulin **1**.



In the course of our synthetic study, we discovered a novel method of converting primary amines to alcohols. Although

(1) Hayashi, T.; Kawasaki, M.; Miwa, Y.; Taga, T.; Morita, N. *Chem. Pharm. Bull.* **1990**, *38*, 945.

(2) For a recent example of the synthesis of other aphidicolans, see: (a) Bélanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285. For a review, see: (b) Toyota, M.; Ihara, M. *Tetrahedron* **1999**, *55*, 5641. For the synthesis of scopadulan diterpenes bearing a similar A/B ring system, see: (c) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626. (d) Tagat, J. R.; McCombie, S. W.; Puar, M. S. *Tetrahedron Lett.* **1996**, *37*, 8459. (e) Tagat, J. R.; Puar, M. S.; McCombie, S. W. *Tetrahedron Lett.* **1996**, *37*, 8463. (f) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031. (g) Fox, M. E.; Li, C.; Marino, P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467.

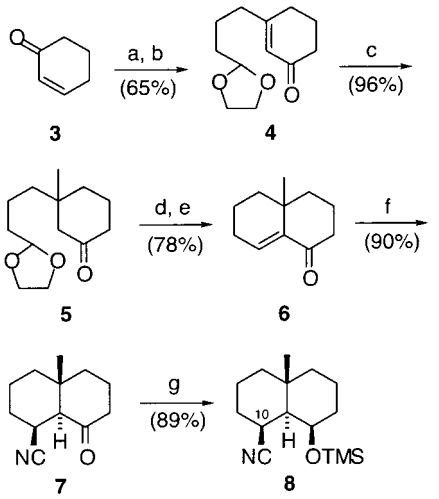
(3) (a) Tanaka, T.; Murakami, K.; Okuda, O.; Inoue, T.; Kuroda, T.; Kamei, K.; Murata, T.; Yoshino, H.; Imanishi, T.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 193. (b) Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.* **1995**, *43*, 1407.

10.1021/ol006334a CCC: $19.00
Published on Web 08/16/2000

conversion of aromatic amines into alcohols via diazonium salts is a well-known process, that of aliphatic amines is relatively rare.[4] Some of these methods require several steps for the efficient conversion or suffer from low yields, which diminishes their synthetic value. However, our newly invented method is synthetically useful, and herein we present an application of the new method to the synthesis of model compound **2** of (±)-scopadulin **1**.

Starting from 2-cyclohexen-1-one **3**, 6-methylbicyclo-[4.4.0]dec-1-en-2-one **6** was synthesized in a straightforward manner as depicted in Scheme 1. Stereoselective cyanation

Scheme 1

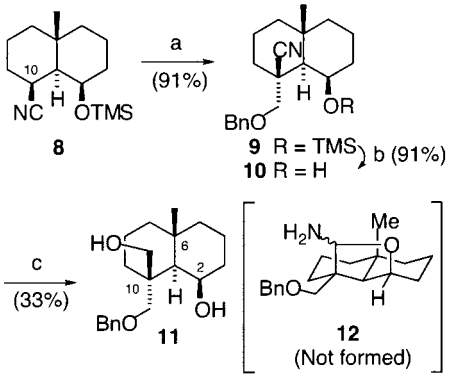


[a] *Reaction conditions*: (a) Li, 2-(3-chloropropyl)-1,3-dioxolane, THF, ultrasound, rt (67%); (b) PCC, Al_2O_3, CH_2Cl_2, rt (97%); (c) Me_2CuLi, Et_2O, −20 → 0 °C (96%); (d) HCl, MeOH, 65 °C; (e) TSA, PhH, dean-stark, 110 °C (78%, 2 steps); (f) Et_2AlCN, TMSCl, PhH, 0 °C (90%); (g) $NaBH_4$, MeOH–THF (2:1), rt (100%); TMSCl, CH_2Cl_2, 0 °C (89%).

of **6** gave the *trans*-fused bicylic ketone **7**.[5] Reduction of the ketone **7** and TMS-protection of the resulting alcohol yielded **8** with the desired stereochemistry.[6]

Next, construction of a quaternary carbon center at C-10 and conversion of the cyano group into a methyl group were investigated (Scheme 2).[7] Treatment of the nitrile **8** with LDA and freshly distilled benzyloxymethyl chloride in THF gave α-alkylated derivative **9**[2g] and subsequent deprotection of the TMS group yielded **10**, both in excellent yields.[6] Our expectation was that the partial reduction of **10** would produce the aminal **12**, followed by a reductive ring-opening

Scheme 2

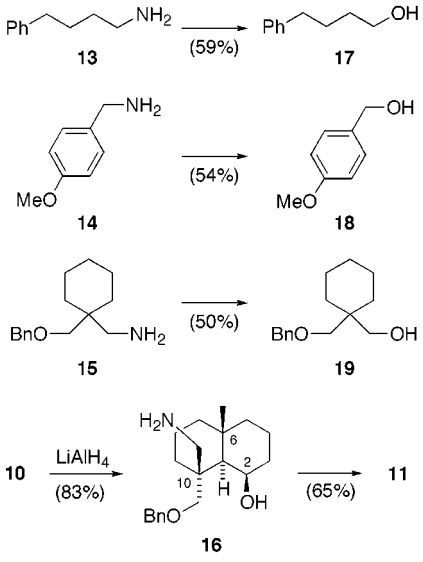


[a] *Reaction conditions*: (a) LDA, BOMCl, THF, −78 → 0 °C; (b) TBAF, THF, 45 °C; (c) i) $LiAlH_4$, THF, −78 → reflux; ii) $H_2N–NH_2·H_2O$, diethylene glycol, 195 °C, then KOH, 210 °C.

reaction under Wolff−Kishner conditions to give the desired 6,10-dimethylated compound.[2f] However, it was not to be the case. Unexpectedly, we isolated diol **11** by $LiAlH_4$-reduction of **10** and subsequent Wolff−Kishner reduction of the crude mixture. Further investigation revealed that the diol **11** was formed from the primary amine derived from **10** by a potassium hydroxide-mediated reaction. All our other efforts to direct reduction of the cyano group to a methyl or formyl group failed.[8,9] Treatment of the nitrile **10** with DIBAL-H led to complete recovery of the starting material, presumably due to steric hindrance.

Accordingly, to reveal the utility of the direct synthesis of the primary alcohols from amines and to optimize the reaction conditions, we briefly investigated the base-mediated reaction using simple amines (Scheme 3). We found that

Scheme 3



[a] *Reaction conditions*: KOH, diethylene glycol, 210 °C.

(4) (a) Whitmore, F. C.; Langlois, D. P. *J. Am. Chem. Soc.* **1932**, *54*, 3441. (b) Streitwieser, A., Jr.; Schaeffer, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 2888. (c) Kotani, R. *J. Org. Chem.* **1965**, *30*, 350. (d) Fujii, T.; Tashiro, M.; Ohara, K.; Kumai, M. *Chem. Pharm. Bull.* **1960**, *8*, 266. (e) Brasen, W. R.; Hauser, C. R. In *Organic Synthethes*; Rabjohn, N., Ed.; John Wiley and Sons: New York, 1963; Collect. Vol. 4, pp 582−584. (f) Katritzky, A. R.; Saba, A.; Patel, R. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1492.

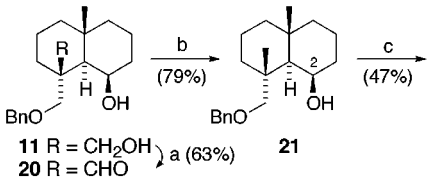
(5) Slight modifications of the published procedures were applied: see ref 2g.

(6) Stereochemistries of **8** and **10** were ascertained by NOE analyses.

the desired conversion proceeded on heating the amine **13** with KOH in diethylene glycol at 210 °C, yielding the alcohol **17** as the sole product. When the other amines **14** and **15** were subjected to this condition, the desired alcohols **18** and **19** were isolated in acceptable yields, respectively. Compound **16**, whose amino group is highly hindered due to the axial 2-hydroxy and 6-methyl groups, similarly gave **11** in 65% yield under identical reaction conditions.[10]

Encouraged by these results, we explored an alternative route via the diol **11**. Modification of functional groups was accomplished as shown in Scheme 4. The primary hydroxy group of **11** was selectively oxidized by $RuCl_2(PPh_3)_3$,[11] and subsequent reduction under Huang-Minlon conditions[12] afforded **21** in good yield. Benzoylation of 2-OH with BzOTf,[13] followed by deprotection of the benzyl group and oxidation, yielded the model compound **2** with all the desired functionalities.

Scheme 4



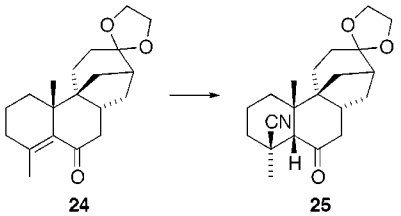
[a] *Reaction conditions*: (a) $RuCl_2(PPh_3)_3$ (0.8 equiv), PhH, rt; (b) K_2CO_3, H_2N–NH_2·H_2O, diethylene glycol, 170 → 210 °C; (c) BzOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) H_2, Pd/C, MeOH, rt; (e) Jones reagent, acetone, rt.

In conclusion, we have demonstrated a novel and efficient method for converting primary amines into alcohols mediated by potassium hydroxide. The new reaction is simple, performed in one step, and applicable to synthesis of sterically hindered 1,4-diols from enones in combination with a cyanation−reduction sequence.[14] Application of this method to the total synthesis of (±)-scopadulin is now being investigated in this laboratory.

Supporting Information Available: Experimental procedures for synthesis of compounds **6**, **7**, **9**, **20**, and **2** as well as ^{1}H NMR spectra for compounds **2**, **4**−**11**, **16**, **20**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006334A

(7) Construction of the quaternary carbon center with the desired stereochemistry has proven to be extremely difficult. Treatment of the β-methylated enone **24** with Et_2AlCN in benzene gave **25** with undesired stereochemistry. Therefore, we planned to introduce a benzyloxymethyl group at C-10 that could be converted into a carboxyl group.



(8) For conversion of the cyano group into a methyl group, see: (a) Kindler, K.; Luhrs, K. *Liebigs Ann. Chem.* **1965**, *685*, 36. (b) Kindler, K.; Luhrs, K. *Ber.* **1966**, *99*, 227.

(9) Attempted conversion of the cyano group into a formyl group using $LiAlH_4$ was also unsuccessful. See: (a) Nagata, W. *Tetrahedron* **1961**, *13*, 287. (b) Nagata, W.; Hirai, S.; Itazaki, H.; Takeda, K. *Liebigs Ann. Chem.* **1961**, *641*, 196. (c) Fry, J. L.; Ott, R. A. *J. Org. Chem.* **1981**, *46*, 602.

(10) Although these reactions were carried out in the presence of air, a similar result was obtained when the reaction was carried out under nitrogen using degassed solvent. Considering these results, the redox mechanism (proceeding through imines) is unlikely. At our current level of understanding, we speculate that the reaction proceeds via a simple nucleophilic substitution of amino group by hydroxide at a high temperature.

(11) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

(12) (a) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487. (b) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301.

(13) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875.

(14) **General procedure for one-step conversion of primary aliphatic amines into alcohols**: **synthesis of (2*R**,6*R**,10*R**)-10-(benzyloxymethyl)-10-(hydroxymethyl)-6-methylbicyclo[4.4.0]decan-2-ol 11.** The amine **16** (10 mg, 0.0315 mmol), KOH (100 mg, 1.75 mmol, excess), and diethylene glycol (0.6 mL) were placed in a round-bottom flask equipped with a refluxing condenser, and the mixture was heated at 210 °C for 3 h.[10] The black solution was then cooled to rt, and Et_2O (2 mL) and H_2O (1.5 mL) were added. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were then washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification of the residue by column chromatography (5:1 hexane/EtOAc) gave 6.5 mg (65%) of the title compound **11**. Recrystallization from hexane/Et_2O provided an analytically pure white solid: mp 139 °C. IR (KBr) cm^{-1}: 3236 (br). ^{1}H NMR ($CDCl_3$, 500 MHz): 1.33 (s, 3H), 1.06−1.59 (m, 11H), 1.84−1.87 (m, 1H), 1.90−1.99 (m, 1H), 3.39 (d, J = 9.0 Hz, 1H), 3.47 (d, J = 12.5 Hz, 1H), 3.48 (d, J = 9.0 Hz, 1H), 4.14 (br s, 2H), 4.20 (s, 1H), 4.21 (d, J = 12.5 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 7.27−7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): 16.9, 18.4, 22.3, 34.6, 35.4, 35.6, 42.7, 44.5, 46.2, 52.2, 66.2, 66.3, 73.5, 78.2, 127.5, 127.6, 128.4, 138.3. MS (FAB) *m*/*z* (%): 319 (MH^+, 25), 91 (100). HRMS (FAB) Calcd for $C_{20}H_{31}O_3$ (MH^+): 319.2273. Found: 319.2269.