Pergamon

Tetrahedron Letters 41 (2000) 1963–1966

TETRAHEDRON LETTERS

The use of L-(+)-tartaric acid in the enantioselective synthesis of isoquinoline alkaloids

Marek Ziółkowski and Zbigniew Czarnocki *

Department of Chemistry, University of Warsaw, Pasteura 1, 02-093, Warsaw, Poland

Received 21 October 1999; accepted 11 January 2000

Abstract

L-(+)-Tartaric acid was used in an enantioselective synthesis of (*S*)-(−)-*N*-acetylcalycotomine.

Keywords: alkaloids; asymmetric synthesis; hydroxy acids; isoquinolines.

Natural tartaric acid ((2*R*,3*R*)-dihydroxybutanedioic acid) has been extensively used as a readily available and effective chiral auxiliary.[1,2] In the chemistry of isoquinolines it is still useful as illustrated by the efficient synthesis of both enantiomers of novel tetracyclic isoquinoline derivatives.[3] Dörnyei and Szãntay[4] were in fact the first in this area. In 1976 they described synthesis of compound **1**, a novel derivative of tartaric acid, that contained the isoquinoline moiety.

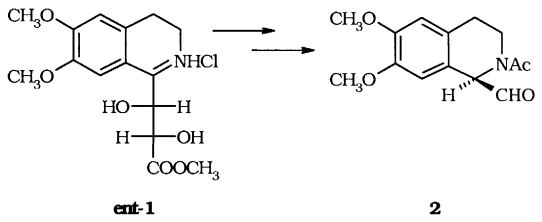
Enantiomer of compound **1** was then further elaborated[5] into aldehyde **2**, from which several isoquinoline alkaloids were obtained (Scheme 1). We have shown that aldehyde **2** could be effectively transformed into 1-benzyltetrahydroisoquinolines, protoberberines, aporphines as well as their homologs, thus being a crucial derivative in the enantioselective synthesis of these types of alkaloids.[5] However, in tartaric acid, which is an efficient chiral inductor, only one asymmetric center was used, the second being sacrificed. The idea of the more effective use of chirality in tartaric acid has focused our interest for a long time and recently we were able to successfully accomplish this task. Also, the fact that the target compound **10** maintains the same C_2 symmetry as the chiral substrate **4**, seemed to be interesting.

Thus, reaction of L-(+)-diethyl tartarate **4** with 3,4-dimethoxyphenylethylamine **3** afforded diamide **5** in nearly quantitative yield. Protection of the hydroxyl groups in **5** by di-*O*-acetylation using acetic anhydride in pyridine afforded ester-amide **6** in 96% isolated yield. Compound **6** was then subjected to several experiments directed towards double Bischler–Napieralski cyclization, but despite prolonged efforts and the use of many reagents and methods we were unable to obtain the desired product.

Eventually, we found that mild conditions, involving the use of PCl_5 at 0°C afforded a very unstable mono-imine derivative, which could not be properly characterized due to its decomposition. Immediate

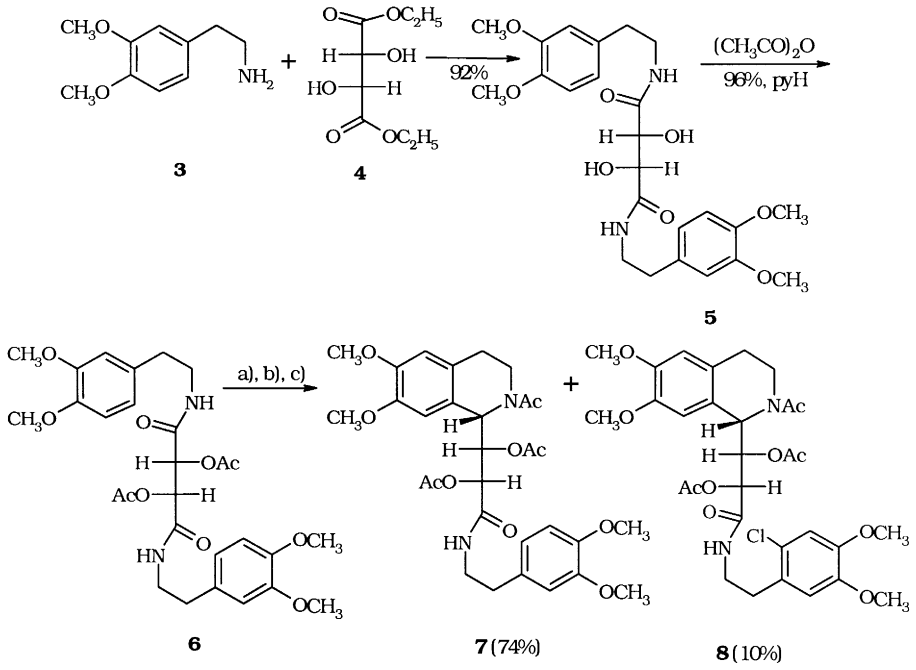
* Corresponding author. Tel: +48 228220211; fax: +48 228225996; e-mail: czarnoz@alfa.chem.uw.edu.pl (Z. Czarnocki)

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00072-1



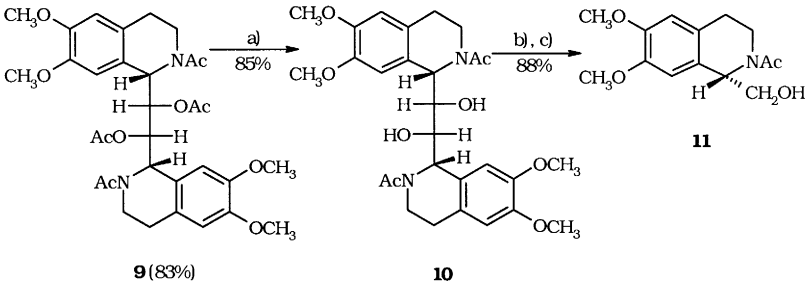
Scheme 1.

reduction and *N*-acetylation of this mono-imine brought about the formation of stable amide **7**. This compound appeared to be diastereomerically pure (by ^{1}H NMR),[6] since the small amount of impurity that contaminated amide **7** turned out to be a chlorination product (**8**) of the activated aromatic ring during a Bischler–Napieralski process (Scheme 2).



Scheme 2. (a) PCl_5, CH_2Cl_2. (b) $NaBH_4$, EtOH. (c) $(CH_3CO)_2O$, pyH

Compound **7** was again subjected to the above three-step reaction sequence, finally giving the desired derivative **9** in 61% yield (from **6**). Again, it was found that this derivative was virtually diastereomerically pure. After removal of both *O*-acetyl groups from **9**, cleavage of the glycol system in **10** with sodium metaperiodate and, finally, reduction of the aldehyde **2** thus formed to the well known[7,8] (*S*)-(−)-*N*-acetylcalycotomine **11**, we accomplished the planned task (Scheme 3). The efficiency of the chiral transfer in the whole sequence seems to be quite good since the yield of **11** was acceptable and its enantiomeric purity (determined by ^{19}F NMR of its Mosher's acid ester[9]) turned out to be >98% ee. We think, therefore that the above described approach may serve as an interesting alternative to existing procedures.



Scheme 3. (a) HCl, reflux. (b) $NaIO_4$, $EtOH/H_2O$. (c) $NaBH_4$, $EtOH/H_2O$

Acknowledgements

This work was supported by the National Committee for Research in the form of a Grant GR-1092/99.

References

1. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1995; p. 940.
2. Inomata, K.; Ukaji, Y. *Rev. Heteroatom. Chem.* **1998**, *18*, 119–140.
3. Lee, J. Y.; Lee, Y. S.; Chung, B. Y.; Park, H. *Tetrahedron* **1997**, *53*, 2449–2458.
4. Dörnyei, G.; Szantay, Cs. *Acta Chim. Acad. Sci. Hung.* **1976**, *89*, 161–168.
5. Czarnocki, Z.; Suh, D.; MacLean, D. B.; Hultin, P.G.; Szarek,W. A. *Can. J. Chem.* **1991**, *70*, 1555–1561 and references cited therein.
6. Preparation of monoamide **7**: To a stirred and cooled to 0°C suspension of 3.9 g (18.7 mmol) of PCl_5 in dry methylene chloride (150 mL) a sample of 5.0 g (8.9 mmol) of acetylamide **6** was added in one portion. After 2 h of stirring at the same temperature, the solution was poured slowly into a suspension of 7.8 g (93.5 mmol) sodium bicarbonate in 100 mL of water. Extraction with chloroform, drying ($MgSO_4$) and evaporation of the solvents gave the residue, which was dissolved in 50 mL of ethanol and subjected to reduction with 2.0 g of $NaBH_4$ added in four portions. After 2 h stirring at the same temperature, ethanol was removed and 50 mL of chloroform and 50 mL of brine was added to the residue. The organic layer was separated and water layer was then extracted with chloroform. Combined organic extracts after drying ($MgSO_4$) were evaporated and residue was dissolved in 50 mL of pyridine and treated with 15 mL of freshly distilled acetic anhydride for 12 h at room temperature. The solvents were evaporated in vacuo and the residue was dissolved in 70 mL of chloroform. The organic phase was washed with 3×50 mL of brine, dried ($MgSO_4$) and concentrated under reduced presure. Column chromatography on Al_2O_3(III) using hexanes/ethyl acetate 1:1 (v/v) allowed the separation of compounds **7** and **8**. Data for amide **7**: yield 74%, mp 196–197.5°C, $[\alpha]_D^{23}$ −48.9 (*c* 1.19, $CHCl_3$). IR (KBr, cm^{-1}): 3400; 2900; 1750; 1650; 1500; 1275; 1200. ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)): 6.81 (s, 1H, H-8); 6.68–6.74 (m, 2H, H-5 and H-9); 6.64 and 6.60 (two s, 1H each, H-5′ and H-8′); 6.04 (t, 1H, J=5.9 Hz, NH); 5.67 (d, 1H, J=9.8 Hz, H-1a); 5.62 (dd, 1H, J_1=9.8 Hz, J_2=2.4 Hz, H-1a′); 5.26 (d, 1H, J=2.4 Hz, H-1′); 3.88, 3.86, 3.84 and 3.84 (four s, 3H each, 4×OCH_3); 3.74 (dd, 2H, J_1=5.4 Hz, J_2=7.8 Hz, 2H-3); 3.58 (ddd, 1H, J_1=6.8 Hz, J_2=13.2 Hz, J_3=6.4 Hz, H-3_{eq}′); 3.37 (ddd, 1H, J_1=5.9 Hz, J_2=13.2 Hz, J_3=6.4 Hz, H-3_{ax}′); 2.95 (dt, 1H, J_1=5.4 Hz, J_2=16.1 Hz, H-4_{eq}); 2.66–2.76 (m, 2H, 2H-4′); 2.86 (dt, 1H, J_1=6.8.0 Hz, J_2=16.1 Hz, H-4_{ax}); 2.21 and 2.10 (two s, 3H each, 2×OAc); 1.84 (s, 3H, NAc). ^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 170.43; 169.93; 168.42; 167.33; 149.18; 148.57; 147.79; 146.88; 130.94; 126.65; 124.82; 120.63; 112.00; 111.76; 111.36; 111.15; 72.21; 72.04; 56.05; 55.97; 55.92; 55.77; 50.20; 41.96; 40.43; 35.18; 27.68; 21.64; 20.97; 20.60. LSIMS (+) 8 kV (%): 587 (45) ($M+H^+$); 527 (12); 467 (4); 262 (16); 246 (76); 234 (100); 192 (59); 107 (28); 81 (41). Data for compound **8**: yield 10%, mp 180–182°C, $[\alpha]_D^{23}$ −44.1 (*c* 1.29, $CHCl_3$). IR (KBr, cm^{-1}): 3400; 2900; 1750; 1650; 1520; 1275; 1200; 1050. ^{1}H NMR (500 MHz, $CDCl_3$, δ (ppm)): 6.85 (s, 1H, H-8); 6.71, 6.65 and 6.60 (three s, 1H each, H-5, H-5′ and H-8′); 6.13 (t, 1H, J=5.5 Hz, NH); 5.69 (d, 1H, J=9.8 Hz, H-1a); 5.64 (dd, 1H, J_1=9.8 Hz, J_2=2.5 Hz, H-1a′); 5.26 (d, 1H, J=2.5 Hz, H-1′); 3.88, 3.86, 3.84 and 3.84 (four s, 3H each, 4×OCH_3); 3.76 (dd, 2H, J_1=5.5 Hz, J_2=7.0 Hz, 2H-3); 3.56 (ddd, 1H, J_1=7.0 Hz, J_2=13.0 Hz, J_3=6.5 Hz, H-3_{eq}′); 3.43 (ddd, 1H, J_1=7.5 Hz, J_2=13.0 Hz, J_3=6.5 Hz, H-3_{ax}′); 2.99 (dt, 1H, J_1=5.5 Hz, J_2=21.5 Hz, H-4_{eq}); 2.86 (dd, 2H, J_1=7.5 Hz, J_2=6.5 Hz, 2H-4′); 2.80 (dt, 1H, J_1=7.0 Hz, J_2=21.0 Hz, H-4_{ax}); 2.25 and 2.10 (two s, 3H each, 2×OAc); 1.85 (s, 3H, NAc). ^{13}C NMR (125 MHz, $CDCl_3$, δ (ppm)): 170.41; 170.00; 168.44; 167.55; 149.58; 148.38; 148.01; 146.89; 127.77; 126.65;

124.82; 124.66; 113.53; 112.55; 111.78; 111.16; 72.19; 72.10; 56.18; 56.16; 56.05; 55.78; 50.20; 41.96; 39.05; 33.00; 27.67; 21.64; 21.00; 20.56. LSIMS (+) 8 kV (%): 621 (82) $(M+H)^+$; 460 (18); 234 (100).

7. All analytical data for **11** were in accordance with those already described.[8]
8. Czarnocki, Z.; Ziółkowski, M.; Leniewski, A.; Maurin, J. K. *Enantiomer* **1999**, *4*, 71–77 and references cited therein.
9. Determination of the enantiomeric composition of (*S*)-(−)-*N*-acetylcalycotomine **11**: Oxalyl chloride (0.12 mL, 1.4 mmol) was added to the solution (*R*)-(+)-MTPA (66 mg, 0.28 mmol) and DMF (0.022 mL, 0.28 mmol) in 12 mL of hexane. After 1 h the mixture was filtered and concentrated in vacuo and the residue was used without further treatment. The solution of (*S*)-(−)-*N*-acetylcalycotomine **11** (20mg, 0.08 mmol), 1 mL of triethylamine and a catalytic amount of 4-dimethylaminopyridine in 3 mL of dichloromethane was treated with Mosher's acid chloride in 3 mL of dichloromethane. The mixture was then stirred for 24 h at room temperature. The organic layer was washed with aqueous solution of tartaric acid (2%), sodium bicarbonate and brine. The water layer was extracted with two portions of chloroform and the combined extracts were dried ($MgSO_4$), evaporated and the residue was filtered through a small pad of silica gel using $CHCl_3$ as eluent. The ^{19}F NMR spectra were recorded at 471 MHz with C_6F_6 as external reference. In ^{19}F NMR spectra, a pair of signals (due to the presence of stable conformers) were observed at −71.18 and −71.54 ppm (*S* enantiomer) with relative intensities 1.00:2.32, *R* enantiomer was not observed. Therefore, the enantiomeric purity of (*S*)-(−)-*N*-acetylcalycotomine **11** exceeds the value of 98% ee.