Enantioselective Desymmetrization of Tropinone Derivatives by Hydroboration

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Received 17 July 2003

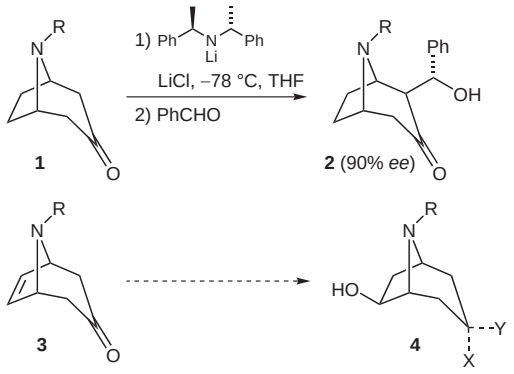
Dedicated to Prof. Larry Overman on the occasion of his 60th birthday.

Abstract: N-Protected tropenone derivatives **3**, prepared from the respective pyrroles **5** and tetrabromoacetone (**6**), were used as starting materials for desymmetrization by hydroboration of the C–C double bond. Hydroboration of **3a** with (–)-$(Ipc)_2BH$ followed by oxidation, however, gave the desired 6-hydroxylated product **4a** only in low yield due to byproduct formation. After acetalization of the carbonyl group in **3**, the corresponding acetals **8** were desymmetrized with $(Ipc)_2BH$ and oxidative workup to chiral alcohols **11** in good yields with excellent enantiomeric excesses in most cases.

Key words: desymmetrization, hydroboration, tropenone, enantioselectivity

Tropane alkaloids represent a class of naturally occurring compounds which have been intensively studied due to their variety of pharmacological activity.[1] Among the most prominent derivatives are atropine, cocaine and scopolamine, and well-known pharmaceuticals such as atrovent® and buscopan® are chemically related to the natural products atropine and scopolamine. The synthesis of tropane derivatives relied mostly on derivatization of the natural compounds, e.g., scopolamine.[2] In contrast, desymmetrization of C_s-symmetrical precursors such as **1** or **3** have been only rarely used. One important example is the enantioselective deprotonation and subsequent aldol reaction of tropinone **1** developed by Simpkins using a chiral lithium amide base as the key step (Scheme 1).[3]

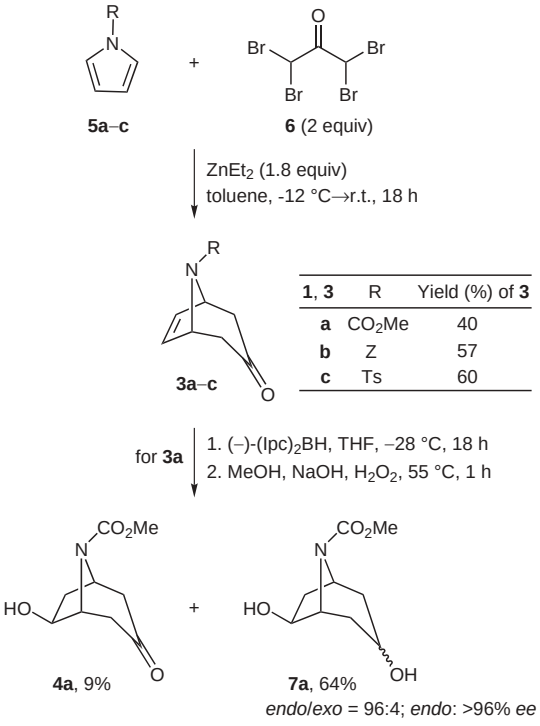
We were interested to investigate if tropenone **3** could be desymmetrized to the chiral alcohol **4** by using enantioselective hydroboration. Up to now hydroboration has been utilized for desymmetrization purposes only in one case. Marchionni and Vogel realized the asymmetric synthesis of complex tricyclic polypropanoates in this way.[4] Thus, it was tempting to investigate desymmetrization via hydroboration for meso alkaloids. The preliminary results towards this goal are reported in this paper.



Scheme 1

As shown in Scheme 2, N-protected tropenones **3** were prepared via [4+3] cycloaddition from pyrroles **5** and tetrabromoacetone (**6**).[5] The required oxyallyl cation was generated from **6** following a methodology developed by Mann.[6] In order to improve the yields, benzene was replaced by toluene as the solvent, and a twofold excess of the oxyallyl component **6** was applied. This modification resulted in decreased reaction temperatures (from 0 °C to –12 °C). Derivatives **3a–c** were isolated in moderate yields of 40–60%.

In an initial attempt functionalization of the double bond by hydroboration was investigated preliminary with the tropenone derivative **3a** (Scheme 2). However, hydroboration of carbamate-protected **3a** with (–)-diisopino-



1, 3	R	Yield (%) of 3
a	CO_2Me	40
b	Z	57
c	Ts	60

Scheme 2

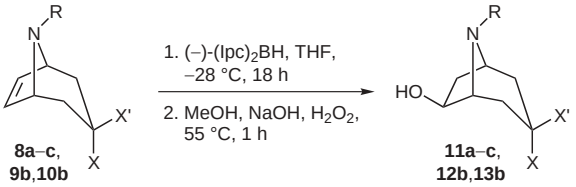
SYNLETT 2003, No. 14, pp 2175–2177
Advanced online publication: 15.10.2003
DOI: 10.1055/s-2003-42080; Art ID: G17403ST.pdf

campheylborane $(Ipc)_2BH$ and subsequent oxidation with H_2O_2 in MeOH/NaOH[7] afforded a mixture of the desired alcohol **4a** in only 9% yield, diastereomeric diols **7a** as major products (*endo*/*exo* = 96:4), and 18% of unreacted starting material **3a**. In contrast to Molander's experiments on acyclic β,γ-unsaturated ketones[8] a hydroboration/intramolecular reduction sequence leading to the diol **7a** is not possible for steric reasons. However, an intermolecular pathway might be conceivable, because Molander demonstrated that alkenes react much faster with dialkylboranes than ketones. The major diastereomer of **7a** could be separated from the minor one by recrystallization from $CHCl_3$, and after derivatization with (*S*)-(+)-Mosher's reagent, an enantiomeric excess of >96% was determined for *endo*-**7a** by NMR spectroscopy.

To avoid the formation of byproducts **7**, the carbonyl group in **3** was protected prior to hydroboration. As outlined in Scheme 3, two different protection strategies, i.e. acetalization and reduction/silylation were used. The acetalization of compound **3a** with ethylene glycol in the presence of catalytic amounts of *p*-TsOH in boiling benzene under Dean–Stark conditions was accompanied by side-reactions, giving the acetal **8a** only in 17% yield. Fortunately, clean acetalization of **3a**–**c** was achieved with pyridinium *p*-toluenesulfonate (PPTS) as a catalyst in boiling benzene. Acetals **8a**, **8b**[9] and **8c** were obtained in high yields of 84–93%.

The reduction/silylation approach was studied for compound **3b** (Scheme 3). Reduction of ketone **3b** with $NaBH_4$ in MeOH[10] and subsequent silylation with *tert*-butyldimethylchlorosilane (TBSCl) and imidazole gave the derivatives **9b** and **10b** in 85% yield in a ratio of **9b**:**10b** = 64:36, which could be separated by chromatography.

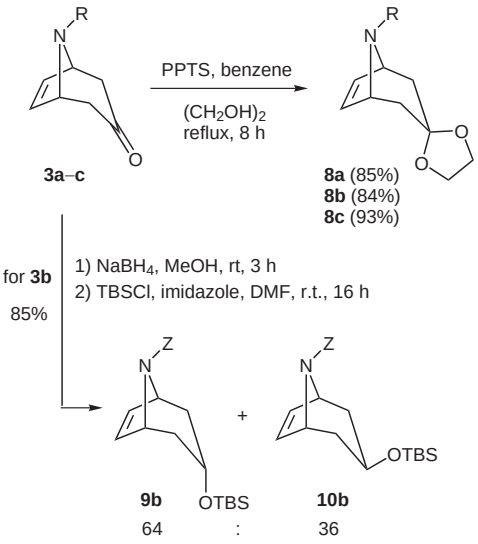
The protected tropenone derivatives **8a**–**c**, **9b** and **10b** were submitted to hydroboration with $(Ipc)_2BH$ in THF at –28 °C as depicted in Scheme 4. After oxidative hydrolysis alcohols **11a**, **11b**[11] and **11c** and **12b**, **13b** were accessible in good yields (72–96%). In the case of **11a** and **11b** the ee-values were determined by GC on a chiral stationary phase.[12] Compounds **11c**, **12b** and **13b** were derivatized with Mosher's reagent,[13] and their enantiomeric excesses were determined by NMR spectroscopy and additionally by GC of the diastereomers.[14] The carbamate- and *Z*-protected tropenone derivatives **11a**,**b** and **12b** gave very high enantioselectivities (>99% ee). The enantiomeric excess of compound **13b** was somewhat decreased to 81%. In contrast, N-tosyl-protected tropenone **11c** displayed only very low enantioselectivity (21% ee). Applying Mosher's method, the absolute configuration of alcohols **11**–**13** was determined to be (*S*).[13] In case of **11c**, X-ray diffraction confirmed this assignment.[15]



Compd	R	X	X'	Yield (%)	*ee* (%)
11a	CO_2Me	OCH_2CH_2O		77	>99
11b	Z	OCH_2CH_2O		96	>99
11c	Ts	OCH_2CH_2O		76	21
12b	Z	OTBS	H	72	>99
13b	Z	H	OTBS	96	81

Scheme 4

The decreased enantioselectivity in the case of the N-tosyl-protected tropenone **8c** is probably caused by steric hindrance of the phenyl ring of the tosyl group, being arranged directly above the double bond, as can be seen from the X-ray crystal structure of **8c** (Figure 1).[15]



Scheme 3

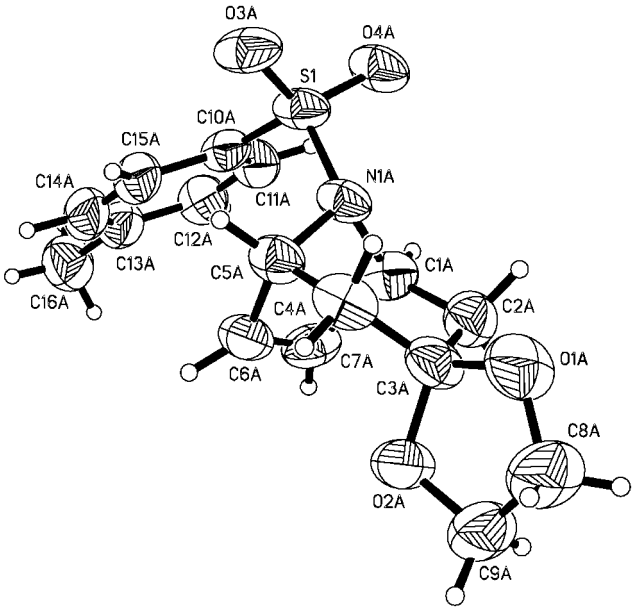


Figure 1 ORTEP view of the N-tosyl protected tropenone derivative **8c**

Thus, during attack of the bulky borane reagent from the *exo*-face interactions with the tosyl group result in a decreased energy difference between diastereomeric transition states (i.e. attack at the *Re* carbon versus *Si* carbon of the double bond). It should be noted that the observed conformation of the N-tosyl group in **8c** is not merely a crystal packing effect, but it is also present in solution, as evidenced by the significant high field shift of the olefinic signals in the ^{1}H NMR spectrum of the tosyl derivative **8c** (δ = 5.68 ppm) compared to the carbamate- and *Z*-protected compounds **8a** (δ = 6.15 ppm) and **8b** (δ = 6.09–6.22 ppm).

In conclusion, desymmetrization of tropenones using (–)-diisopinocampheylborane followed by oxidation gave convenient access to chiral tropinone derivatives.

Acknowledgment

This work was generously supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Wissenschaftsministerium des Landes Baden-Württemberg.

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(9) ***N*-Benzyloxycarbonyl-spiro{8-azabicyclo[3.2.1]oct-6-ene-3,2′-[1,3]dioxolane} (8b).** A solution of **3b** (5.63 g, 21.9 mmol), ethylene glycol (15 mL) and PPTS (0.8 g, 2.3 mmol) in benzene (200 mL) was heated under Dean–Stark conditions at reflux for 8 h. The reaction mixture was then diluted with EtOAc (250 mL) and washed with H_2O and a solution of NaCl (100 mL each). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography on SiO_2 with EtOAc/hexanes, 3:1 (R_f = 0.14) gave 3.49 g (84% referred to conversion) of **8b** and 2.11 g of unreacted **3b**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (dd, *J* = 13.7 Hz, *J* = 5.3 Hz, 2 H, 2-H_{eq},4-H_{eq}), 2.10 (dd, *J* = 13.7 Hz, *J* = 3.4 Hz, 1 H, 2-H_{ax}), 2.21 (dd, *J* = 13.7 Hz, *J* = 3.4 Hz, 1 H, 4-H_{ax}), 3.75–3.92 (m, 4 H, OCH_2), 4.65 (br, 1 H, 5-H), 4.70 (br, 1 H, 1-H), 5.12 (d, *J* = 12.1 Hz, 1 H, CH_2Ar), 5.19 (d, *J* = 12.1 Hz, 1 H, CH_2Ar), 6.09–6.22 (br m, 2 H, 6-H, 7-H), 7.27–7.38 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.6, 39.5 (C-2, C-4), 56.4 (C-1, C-5), 63.2, 64.3 (OCH_2), 66.7 (CH_2Ar), 106.9 (C-3), 127.8, 127.9, 128.4 (Ar), 132.5, 132.9 (C-6, C-7), 136.6 (Ar), 152.2 (CO) ppm. FT-IR (ATR): 2958 (m), 2926 (m), 2881 (m), 2360 (m), 2341 (m), 1695 (vs), 1411 (s), 1345 (s), 1300 (vs), 1088 (vs)cm^{-1}. MS (EI): *m/z* (%) = 301 (15) [M^+], 257 (10) [$M^+ - C_2H_6O_2$], 170 (10), 91 (100) [$C_7H_7^+$]. Anal. Calcd for $C_{17}H_{19}NO_4$ (301.3): C, 67.76; H, 6.36; N, 4.65. Found: C, 67.56; H, 6.44; N, 4.60.
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(11) **(–)-*N*-Benzyloxycarbonyl-6-*exo*-hydroxy-{spiro-8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane} (11b).** A solution of **8b** (5.08 mg, 16.88 mmol) in absolute THF (8 mL) was added at –28 °C to crystalline $(Ipc)_2BH$ (7.4 g, 25.96 mmol), and the reaction mixture stirred at –28 °C for 18 h. After hydrolysis of excess borane with MeOH (2.3 mL), a 3 N NaOH solution (10 mL) and 30% H_2O_2 (10.7 mL) were added and the reaction mixture heated to 55 °C with vigorous stirring. EtOAc (100 mL) was added and the solution washed with a NaCl solution (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on SiO_2 (EtOAc) (R_f = 0.55) gave 5.21 g (96%) of **11b** as a colorless solid. Mp 112 °C (*i*-Pr_2O/CH_2Cl_2), $[\alpha]_D^{20}$ = –8.2 (*c* 1.0, $CHCl_3$), >99% ee. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.78 (br m, 2 H, 2-H_{eq},4-H_{eq}), 1.79–2.08 (br m, 4 H, O*H*, 2-H_{ax},4-H_{ax},7-H_{exo}), 2.65 (dd, *J* = 13.4 Hz, *J* = 7.0 Hz, 1 H, 7-H_{endo}), 3.75–3.85 (m, 2 H, OCH_2), 3.90–3.95 (m, 2 H, OCH_2), 4.15 (br, 1 H, 1-H), 4.44 (br, 1 H, 5-H), 4.54 (br t, *J* = 5.7 Hz, 1 H, 6-H), 5.13 (s, 2 H, CH_2Ar), 7.28–7.37 (m, 5 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.1 (br, C-2), 39.7 (br, C-4), 40.3 (br, C-7), 53.3 (CH_2Ar), 62.3 (C-1), 63.4, 64.5 (OCH_2), 67.0 (C-5), 73.8 (br, C-6), 106.8 (C-3), 127.9, 128.0, 128.5, 136.6 (Ar), 154.2 (CO) ppm. FT-IR (ATR): 3375 (s), 3288 (s), 2950 (s), 2874 (s), 2360 (vs), 2341 (vs), 1699 (vs), 1654 (vs), 1442 (s), 1408 (s), 1108 (vs), 1063 (s)cm^{-1}. MS (EI): m/z (%) = 319 (8) [M^+], 228 (30) [M^+ – benzyl], 184 (20), [M^+ – Z], 140 (15), 98 (20), 91 (100) [$C_7H_7^+$]. Anal. Calcd for $C_{17}H_{21}NO_5$ (319.4): C, 63.94; H, 6.63; N, 4.39. Found: C, 63.94; H, 6.67; N, 4.30.
(12) GC was performed on a Bondex unβ column (20 m × 0.25 mm) with 0.4 bar H_2 as carrier gas. Compound **11a**: temperature program: 3 min at 60 °C, then 1 °C min^{-1} gradient to 200 °C, t_R(*R*-**11a**) = 106.35 min, t_R(*S*-**11a**) = 107.26 min, >99% ee. Compound **11b**: temperature program: 3 min at 150 °C, then 2.5 °C min^{-1} gradient to 200 °C, t_R(*R*-**11b**) = 49.32 min, t_R(*S*-**11b**) = 49.93 min, >99% ee.
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(14) GC was performed on a HP-5 TA column (30 m × 0.32 mm) with a temperature program: 16 °C min^{-1} gradient from 80 °C to 300 °C. Compound **12b**: t_R(*R*-**12b**) = 19.54 min, t_R(*S*-**12b**) = 19.62 min, >99% ee. Compound **13b**: t_R(*R*-**13b**) = 19.85 min, t_R(*S*-**13b**) = 19.99 min, 81% ee.
(15) CCDC 215377(**11a**), CCDC 215376(**8c**) and CCDC 217879(**11c**) contain the supplementary crystallographic data of these structures. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].