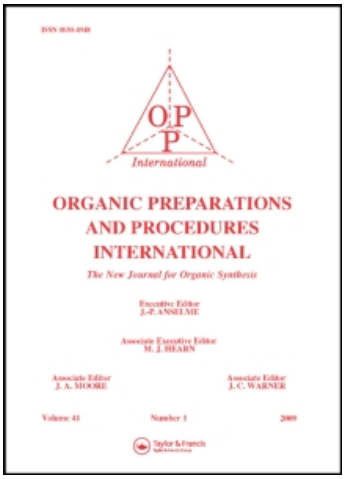

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AN IMPROVED PREPARATION OF (S)-*N*-(BOC)-CYCLOHEXYLALANINAL. THE MOFFAT-SWERN OXIDATION OF α-AMINOALCOHOLS

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AN IMPROVED PREPARATION OF (S)-*N*-(BOC)-CYCLOHEXYLALANINAL. THE MOFFAT-SWERN OXIDATION OF α-AMINOALCOHOLS

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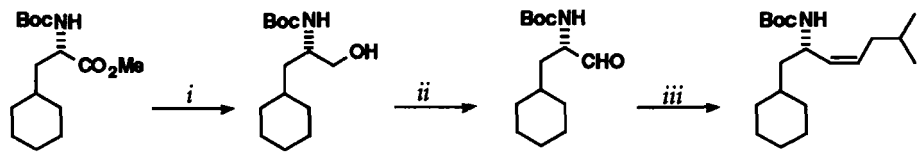
(2S)-*N*-(Boc)-cyclohexylalaninal (**3**) is an important starting material of particular utility in the construction of peptide isosteres related to the renin-angiotensin system; it has been utilized by many research groups involved in the design and synthesis of peptidomimetic therapeutic agents.[1] Inasmuch as α-aminoaldehydes are notoriously prone to racemization, it is not surprising that the synthesis of **3** with a high level of enantiomeric purity has been a somewhat capricious endeavor.[2] Accordingly, there have been numerous approaches to α-aminoaldehydes reported in the literature which have addressed the problem with varying degrees of success.[3] As part of a development project in our laboratory, we required an efficient preparation of **3** which was amenable to large scale synthesis and which delivered consistently high levels of enantiomeric purity. Described herein are our studies on the Moffatt-Swern oxidation of (2S)-*N*-(Boc)-cyclohexylalaninol **2** which culminated in a greatly improved preparation of **3**.



1 **2** **3** **4**

i) $NaBH_4$, AcOH in THF, 0°, 95% *ii*) $(COCl)_2$, *i*-Pr_2EtN, DMSO, CH_2Cl_2, -20°
iii) $Me_2CHCH_2CH_2Ph_3P^+ Br^-$, *t*-BuOK, 0°, THF, 60% overall for steps *ii* and *iii*.

Our initial attempts at the conversion of (2S)-*N*-Boc-cyclohexylalanine methyl ester **1** directly to the corresponding aldehyde by partial reduction with aluminum-based reagents gave unsatisfactory results upon scale-up and led us to consider a two-step reduction/oxidation sequence. As shown in the equation, **1** was converted to **2** by reduction with $NaBH_4$/AcOH/THF in near quantitative yield (>98%). With **2** in hand, a survey of DMSO-based[4] oxidation protocols was undertaken; the results of which are presented in the Table. The various oxidation reactions were performed on 0.1-1.0+ mole

scale and were easily monitored by gas chromatography (see Experimental Section). The enantiomeric excess (e.e.) of the resultant α-amino-aldehyde **1** was determined by $NaBH_4$/EtOH reduction of the crude aldehyde back to **3**, derivatization with either 3,5-dinitrophenylisocyanate or Mosher's acid, and assay by either chiral HPLC (DNP derivatives) or GC (Mosher's esters). Due to the instability of α-aminoaldehydes during purification, **1** was used directly in subsequent reactions (typically 90-95% pure by GC).

As an indication of the chemical efficiency of the oxidations, the two-step conversion of **2** to allylic amine **4** (35/1, Z/E) proceeded in 60% yield overall.[5] Additionally, **3** is configurationally stable at -20° in the absence of trace acid or base for at least three weeks and will stand overnight heating at 30° without racemization. However, heating at 50° for 12 hrs reduced the e.e. of a sample from 94% to 83%.

TABLE. Oxidation of (2S)-N-(Boc)-cyclohexylalaninol. Optimization of e.e.

Entry	Activator	Base	Bath Temp.	Rxn. Temp.[a]	e.e.(%)
1	$(COCl)_2$	Et_3N	< -70°	-40°	66%
2	$(COCl)_2$	Et_3N	< -70°	< -70°	94%
3	$(COCl)_2$	$(i\text{-}Pr)_2NEt$	-20°	-15°	> 95%
4	$Pyr{\bullet}SO_3$	Et_3N	0°	30°	33%[b]
5	$Pyr{\bullet}SO_3$	Et_3N	0°	30°	> 95%[c]

a) Maximum internal reaction temperature; b) A mixture of $Pyr{\bullet}SO_3$ was added slowly to a DMSO solution of Et_3N and **2**; c) Addition of a dichloromethane solution of $Et_3N/Pyr{\bullet}SO_3$ to a dichloromethane solution of DMSO and **2**.

Both the Swern and the Doering modifications of the original Moffat oxidation were examined. In the case of the Swern oxidation, the traditional $(COCl)_2$/DMSO/Et_3N system proved to be extremely sensitive to the internal temperature of the reaction mixture. Entry 1 of the Table for example, represents an experiment in which a solution of triethylamine in dichloromethane at room temperature was added to a solution of oxalyl chloride, dimethylsulfoxide and **2** in dichloromethane at -70°. Within minutes of initiation, the internal temperature rapidly rose to -40° and, after completion of the addition, **1** was isolated with an e.e. of only 66%.[6] Alternatively (entry 2), addition of a precooled (-70°) solution of triethylamine in the same solvent provided **1** with an e.e. of 94%, after an inverse, low temperature quench with 10% aqueous citric acid. Acceptable results (entry 3) may also be obtained at much warmer temperatures (up to -15° internal temperature) by simply replacing the triethylamine with diisopropylethylamine (Hunig's base); the oxidation with Hunig's base proceeds more slowly but is equivalent in terms of chemical yield and enantiomeric excess.[7]

Use of the Parikh-Doering oxidation also gave acceptable levels of enantiopurity provided certain precautions were taken.[8] Application of the standard procedure for pyridine-sulfur trioxide oxidations (entry 4) in which a dimethylsulfoxide solution of $Pyr{\bullet}SO_3$ is slowly added to a dimethyl-

sulfoxide solution of **2** and triethylamine leads to unacceptable levels of racemization. The poor e.e. was thought to be due to the long contact time between **3** and free triethylamine present at low conversion. Based upon this idea, an improved procedure involving the addition of a pre-mixed solution of triethylamine and Pyr•SO_3 in dichloromethane to a dichloromethane solution of dimethylsulfoxide and **2** was developed; this protocol provided **3** with an e.e. of >95%. A drawback to the Pyr•SO_3-based method is that ca. 10-15% of the methylthiomethyl ether of **2** is formed as a side-product.[9]

In summary, three procedures have been described for the large scale preparation of highly enantio-enriched (S)-*N*-(Boc)-cyclohexylalaninal. The most practical method appears to be the Swern modification using Hunig's base, although the other two methods are also quite serviceable.

EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere in undried glassware. Solvents and reagents were obtained from commercial sources and were used as received without further purification. Gas chromatograms were recorded on a Hewlet Packard HP 5890 instrument equipped with an Alltech AT-1 column. Determinations of enantiomeric purity based on chiral HPLC were made on a Spectra Physics SP8800 instrument using a Regis Pirkle Covalent D-2-napthylalanine column. ^1H and ^{13}C NMR were recorded on a GE QE300 spectrometer at 300 MHz and 74.8 MHz respectively and are referenced to internal TMS (0.00 ppm). All reported temperatures refer to internal temperatures of the reaction mixtures unless otherwise indicated. Compounds **2**, **3**, and **4** displayed spectral (^1H, ^{13}C, IR, and MS) data consistent with that previously reported in the literature.[1c]

(2S)-*N*-Boc-Cyclohexylalaninol (2).- A 2L round bottom flask equipped with a nitrogen inlet, an addition funnel, and a mechanical stirrer (mechanical stirring is advised, particularly with large scale preparations because the precipitation of boron salts during the quench leads to a thick slurry) was charged with **1** (100.0 g, 0.35 mol, 1.0 equiv), tetrahydrofuran (270 mL) and sodium borohydride (53.1 g, 1.44 mol, 4.1 equiv). The suspension was treated with glacial acetic acid (86.0 g, 1.44 mol, 4.1 equiv) in a dropwise fashion over a five hour period; the internal reaction temperature was maintained below 35°. The mixture was stirred an additional 16 hr after the addition was complete. The mixture was cooled to 15° (bath temperature) and *carefully* quenched with water (750 mL, with the initial 5 mL added over a 1 hr period). At an intermediate stage in the quench, the mixture became quite thick but as the quench was continued the salts dissolved. The mixture was then concentrated on the rotary evaporator to a thick white paste. The paste was suspended in ethyl acetate (700 mL) and filtered to remove the solids. The cake was washed with additional ethyl acetate (2 x 100 mL) and the combined washes were placed in a separatory funnel. The upper organic phase was removed and the aqueous phase was washed with ethyl acetate (400 mL). The combined organics were finally washed with 10% aqueous sodium chloride (600 mL), dried with magnesium sulfate, and concentrated *in vacuo* to give **2** as a thick, colorless oil containing ca. 10% ethyl acetate (yield, 94.9 g, 95%). ^1H NMR ($CDCl_3$) 4.72 (1H, d, J = 7.5 Hz), 3.73 (1H, broad multiplet), 3.65 (1H, dd, J = 4.5, 10.5 Hz), 3.49 (1H, dd, J = 6.0, 10.5 Hz), 2.82 (1H, broad singlet), 1.81 (2H, broad doublet), 1.75-1.60 (5H, m), 1.45 (9H, s), 1.35-1.15 (6H, m). ^{13}C NMR ($CDCl_3$) 156.62, 60.03, 34.10, 33.72, 28.32, 26.45, 26.24, 26.11.

IR (nujol mull): 3357, 2921, 2844, 1692, 1517, 1452 cm^{-1}.

(2S)-*N*-Boc-Cyclohexylalaninal (3). Method A: Oxalyl Chloride-Triethylamine.- A 500 mL round bottom flask equipped with a nitrogen inlet, an addition funnel, a thermometer, and a magnetic stirbar was charged with oxalyl chloride (6.26 g, 0.049 mol, 1.26 equiv) and dichloromethane (190 mL). The solution was cooled to -78° with a carbon dioxide/methanol bath. While maintaining the internal temperature below -60°, a dichloromethane (5.5 mL) solution of dimethylsulfoxide (6.54 g, 0.078 mol, 2.0 equiv) was added followed by a dichloromethane (34 mL) solution of **2** (10.0 g, 0.0389 mol, 1.0 equiv). A pre-cooled (-70°) dichloromethane (55 mL) solution of triethylamine (11.8 g, 0.117 mol, 3.0 equiv) was added at a rate which maintained the internal reaction temperature below-70°. The reaction was allowed to stir at -70° for two hours after the addition was complete; after which time, GC analysis showed the reaction to be complete. The mixture was then transfered by cannula into a 20% aqueous solution of citric acid (160 mL). After the biphasic system had reached ambient temperature, the lower, organic phase was removed in a separatory funnel and the remaining aqueous phase was washed with additional dichloromethane (160 mL). The combined organics were washed with water (200 mL) and dried over sodium sulfate before being stripped of volatiles on a rotary evaporator (bath temperature < 30°) to give **3** as a pale yellow oil (crude yield: 10.1 g, >90% **3** by GC). $[\alpha]^{25} = -22.6$ (c = 2, MeOH). ^1H NMR ($CDCl_3$) 9.58 (1H, s), 4.91 (1H, broad mult), 4.27 (1H, broad mult), 1.83 (2H, broad doublet), 1.78-1.62 (6H, mult), 1.45 (9H, s), 1.40-1.15 (5H, mult). ^{13}C NMR ($CDCl_3$) 200.48, 36.73, 33.87, 33.80, 32.59, 28.27, 26.30, 26.17, 26.02. IR (thin film) 3335, 2932, 2844, 1719, 1692, 1507, 1447 cm^{-1}. MS (EI) *m/e* (rel. int.) 226 (M^+-31, 47), 184 (22), 170 (100), 126 (90), 109 (25), 88 (28).

Method B: Oxalyl Chloride-Diisopropylethylamine.- A 500 mL round bottom flask equipped with a nitrogen inlet, an addition funnel, a thermometer, and a magnetic stirbar was charged with oxalyl chloride (6.26 g, 0.049 mol, 1.26 equiv) and dichloromethane (50 mL). The solution was cooled to -30° with a 30% aqueous calcium chloride/carbon dioxide slush and treated with a dichloromethane (5 mL) solution of dimethylsulfoxide (6.54 g, 0.078 mol, 2.0 equiv). The reaction was stirred for 0.5 hr while gas evolved. A dichloromethane (30 mL) solution of **2** (10.0 g, 0.039 mol, 1.0 equiv) was then added in a dropwise fashion (internal temperature was maintained below -15°). The resulting cloudy suspension was stirred at -20° for one hour and then treated with a dichloromethane (50 mL) solution of diisopropylethylamine (15.1 g, 0.117 mol, 3.0 equiv) over a 40 minute period (internal temperature was maintained below -15°). The reaction was followed by GC and after 1.5 hr no remaining starting material was detected. The mixture was poured into a 20% aqueous citric acid solution (150 mL), stirred for 0.5 hr, and transferred to a separatory funnel. The lower, organic phase was removed and the upper, aqueous phase was washed with additional dichloromethane (100 mL). The combined organics were washed with water (200 mL), dried with sodium sulfate, and stripped of volatiles on a rotary evaporator (bath temperature < 30°) to give **3** as a pale yellow oil (crude yield 9.8 g, >90 % **3** by GC).

Method C: Pyr•SO_3-Triethylamine.- A 3L, round bottom flask equipped with a nitrogen inlet, mechanical stirring mechanism, and an addition funnel was charged with **2** (79.9 g, 0.31 mol, 1.0

equiv), dimethylsulfoxide (110 mL), and dichloromethane (240 mL). A second 2L, round bottom flask equipped as above was charged with pyridine·sulfur trioxide complex (125.0 g, 0.79 mol). An additional amount of dimethylsulfoxide (330 mL) was added and the solution was cooled to 0° (bath temperature). Triethylamine (83.2 g, 0.79 mol, 2.5 equiv) was added to the pyridine·sulfur trioxide solution over a 20 minute period. The solution was stirred for one hour and then added to the solution of **2** via cannula over a 1.5 hr period. The reaction was complete (by GC assay) upon completion of addition; the mixture was, however, stirred an additional one hour before being poured into a 20% aqueous citric acid solution (1L). The mixture was diluted with additional dichloromethane (400 mL) and transfered to a separatory funnel. The organic layer was removed and the aqueous layer was washed with dichloromethane (900 mL). The combined with organics were washed with 20% aqueous citric acid (1 x 1L), water (1 x 1L), and dried over sodium sulfate before being stripped of volatiles on a rotary evaporator (bath temperature < 30°). This provided **1** as an 80% pure (by GC and ^{1}H NMR) pale yellow oil contaminated with ca. 15% of the methylthiomethyl ether of **2**. This impurity did not affect the material's subsequent utilization.

Determination of Enantiomeric Excess (e.e.).- A sample of **1** (0.5 g) was placed in a 50 mL round bottom flask with a magnetic stirrer and dissolved in ethanol (15 mL). The solution was treated with excess sodium borohydride (0.2 g) as a solid in a portionwise fashion and stirred for 30 minutes, at which time, the reaction was quenched by the slow addition of 20% aqueous citric acid (15 mL). The mixture was transfered to a separatory funnel and extracted with ethyl acetate (2 x 30 mL). The combined organics were washed with water (35 mL), dried with sodium sulfate, and concentrated to give **2** as a thick, colorless oil.

3,5-Dinitrobenzoyl azide (0.33 g) was charged to a 100 mL round bottom flask and dissolved in toluene (20 mL). The flask was equipped with a condenser and the solution was brought to reflux and held for 1.5 hr. The mixture was then allowed to cool to ambient temperature and an aliquot (10 mL) was removed by pipette. The aliquot was added to a toluene (5 mL) solution of **2** (0.18 g) and stirred for 1 hr. An aliquot (ca. 0.5 mL) of this mixture was then removed, quenched with ethanol (2 mL), and assayed by chiral HPLC using a Regis Pirkle Covalent D-2-napthylalanine column with a dichloromethane/isopropanol/heptane (2/10/88) solution as eluent. Retention times: (S)-isomer, 3.47 min; (R)-isomer, 3.75 min.

(2S)-*N*-Boc-2-amino-1-cyclohexyl-6-methyl-3(Z)-heptene (4).- A 500 mL round bottom flask equipped with a nitrogen inlet, an addition funnel, a thermometer, and a magnetic stirbar was charged with isoamyltriphenylphosphonium bromide (44.2 g, 0.107 mol, 1.3 equiv) and tetrahydrofuran (100 mL). The suspension was cooled with an ice/methanol bath to an internal temperature of -10° before being treated with solid potassium *tert*-butoxide (13.8 g, 0.123 mol, 1.5 equiv). The reaction mixture turned deep red and was stirred at -10° for 6 hrs. The mixture was then treated with a tetrahydrofuran (50 mL) solution of **1** (20.9 g, 0.082 mol, 1.0 equiv) in a dropwise fashion over a 0.5 hr period (internal temperature was maintained below 0°). The reaction was judged complete after 0.5 hr by GC analysis for disappearance of starting material. The mixture was poured into ice cold 20% aqueous

citric acid (200 mL) and allowed to warm to room temperature. The mixture was extracted with heptane (300 mL) and the organic layer was washed with 90/10 dimethylformamide/water solution (3 X 150 mL). The resulting heptane extracts were concentrated to give **4** as an off white, waxy solid (18.0 g, 71%, 35:1 mixture of Z:E isomers). mp. 55°, $[\alpha]^{25}$ = +48.8° (c = 1, CH_3OH), ^1H NMR ($CDCl_3$) 5.45 (d of t, 1H, J = 10.8, 7.5 Hz) 5.18 (q of t, 1H, J = 15.0, 9.0, 7.5 Hz), 4.50-4.30 (overlapping multiplets, 2H), 2.03 (t, 2H, J = 7.5 Hz), 1.80-1.55 (multiplet, 7H), 1.43 (s, 9H), 1.30-1.10 (m, 7H), 0.91 (d, 3H, J = 3.0 Hz), 0.85 (d, 3H, J = 3.0 Hz). ^{13}C NMR ($CDCl_3$) 131.8, 44.2, 36.79, 34.17, 33.53, 33.51, 28.59, 28.45, 26.57, 26.28, 22.41, 22.33. IR (thin film) 3346, 2975, 2899, 1703, 1517, 1458, 1370 cm^{-1}. MS *m/e*, (relative intensity) 310 (M^+1, 78.9), 271 (100), 254 (18.0), 210 (37.7). HRMS (FAB) Calcd for $C_{19}H_{36}NO_2$: 310.2745; Found: 310.2835.

Determination of Enantiomeric Excess of 4. A 50 mL round bottom flask equipped with a magnetic stirbar was charged with **4** (0.4 g, 1.3 mmol, 1.0 equiv) and treated with a 4/1 (v/v) solution of acetic acid and concentrated hydrochloric acid (6 mL). The suspension was stirred for 1 hr during which time gas evolved and the solids dissolved. TLC analysis (dichloromethane, **4** R_f = 0.56) showed no remaining starting material and the reaction mixture was poured into water (100 mL). The pH was adjusted to 13 with 50% sodium hydroxide and the cloudy suspension was extracted with dichloromethane (100 mL). The organic layer was washed with water (50 mL) and concentrated to a thick, oily residue. The residue was taken-up in toluene (15 mL) and treated with a 10% aqueous solution of sodium carbonate (5 mL) followed by 3,5-dinitrobenzoyl choride (0.32 g, 1.4 mmol, 1.0 equiv). The biphasic mixture was stirred for 1 hr, quenched with methanol (ca. 2 mL), and an aliquot (ca. 0.5 mL) was removed and diluted prior to assay. Chiral HPLC analysis using a Regis Pirkle Covalent D-2-napthylalanine column with a dichloromethane/isopropanol/heptane (2/10/88) solution as eluent showed a 92% e.e. for **4** (96/4). Retention times: (S)-isomer: 10.66 min.; (R) isomer: 13.56 min.

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REFERENCES

1. a) H. D. Kleinert, *Am. J. Hypertens.* **2**, 800 (1967); b) J. R. Luly, N. Ba Maung, J. L. Soderquist, A. K. L. Fung, H. D. Stein, H. D. Klienert, P. A. Marcotte, D. A. Egan, B. Bopp, I. Merits, G. Bolis, J. Greer, T. J. Perun.and J. J. Plattner, *J. Med. Chem.*, **31**, 2264 (1988); c) J. R. Luly, C.-N. Hsiao, N. Ba Maung and J. J. Plattner, *J. Org. Chem.*, **53**, 6109 (1988); d) R. A. Rivero and W . J. Greenlee, *Tetrahedron Lett.*, **32**, 2453 (1992).

2. It has been our experience that many methods are effective for the small scale production of α-amino-aldehydes of high enantiopurity, scale-up of these procedures, however, typically provided material of greatly reduced enantiopurity due to the various technical problems discussed in the following text.

3. a) J. Jurczak and A. Golebiowski, *Chem. Rev.*, **89**, 149 (1989); b) For previous reports on the synthesis of **1** see reference 1c and J. R. Luly, J. F. Dellaria, J. J. Plattner, J. L. Soderquist and Y. Yi, *J. Org. Chem.*, **52**, 1487 (1987); c) M. R. Leanna, H. E. Morton and T. J. Sowin, *Tetrahedron Lett.*, **32**, 5029 (1992).

4. a) A. J. Manusco and D. Swern, *Synthesis*, 165 (**1981**); b) T. T. Tidwell, *Org. React.*, **39**, 297 (1990).

5. See reference 1c for original synthesis of **4**.

6. Similar findings were recently reported: A. E. DeCamp, A. T. Kawaguchi, R. P. Volante and I. Shinkai, *Tetrahedron Lett.*, **32**, 1867 (1991). The racemization problem encountered by these workers was solved by a low temperature quench of the reaction mixture with acetic acid.

7. (a) Hunig's base has been used in the Moffat Swern oxidation of (*S*)-phenylglycinol to its corresponding, configurationably labile, α-amino-aldehyde: J.-N. Denis, A. Correa and A. E. Greene, *J. Org. Chem.*, **56**, 6939 (1991) and references therein.

8. a) J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967); b) Y. Hamada and T. Shioiri, *Chem. Pharm. Bull. Jpn*, **30**, 1921 (1982).

9. This is undoubtedly due to the generation of the corresponding sulfur ylide during the pre-reaction mixing of pyridine-sulfur trioxide complex with triethylamine (see ref. 4 for a discussion of the side reactions of this process).

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