Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2177–2180

TETRAHEDRON: *ASYMMETRY*

On the absolute stereochemistry of (–)-4-alkylnonan-2-ones

Victor Garcia-Ruiz and Simon Woodward*

School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK

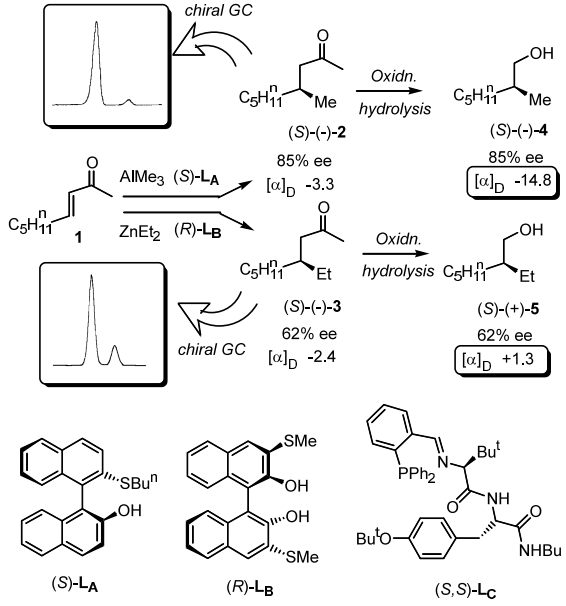
Received 4 September 2002; accepted 11 September 2002

Abstract—The alcohols (*S*)-$C_5H_{11}{}^nCH(R)CH_2OH$ (R = Me, Et) have been prepared by Evans' alkylation chemistry (>98% e.e.). For R = Me $[\alpha]_D = -15.5$ (*c* 0.31, MeOH); for R = Et $[\alpha]_D = +6.8$ (*c* 0.31, MeOH). Equivalent alcohols are obtained by Baeyer–Villiger oxidative cleavage of (*S*)-(–)-$C_5H_{11}{}^nCH(R)CH_2COMe$ (R = Me, 85% e.e.; R = Et, 62% e.e.) derived from catalytic asymmetric conjugate addition. Thus, $AlMe_3$ or $ZnEt_2$ addition to the *Si* face of the enone generates a (–) antipode with a 4*S* stereocentre.

1. Introduction

Previously, we have presented copper(I)-catalysed additions of $AlMe_3$ and $ZnEt_2$ using chiral thioether ligands L_A[1]and $\mathbf{L_B}$[2,3] and have often employed (*E*)-non-3-en-2-one **1** as a standard test substrate (Scheme 1, in part). We assigned[1] the (–) antipode of the methyl addition product to be (*S*)-**2** based on its degradation to 2-methylheptan-1-ol **4** and subsequent comparison of the chiroptical data to literature values for (*S*)-(–)-**4**.[4] Based on the GC elution order of the analogous ethyl addition product **3** on the same *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin[5] column as **2** we *tentatively* assigned (–)-**3** to also have (*S*) stereochemistry. This deduction is not satisfactory for a number of reasons: Firstly, full experimental details on the purity and preparation of literature (*S*)-(–)-**4** are not available.[4] Secondly, the $Na_2S_2O_8$-based Baeyer–Villiger oxidation we used to obtain our sample of (*S*)-(–)-**4**[1] was inefficient and could not be used in the degradation of the equivalent ethyl compound. Thirdly, the assumption that the chiral GC elution order predicts the stereochemistry may not be correct. Finally, we included a typographical error in the ligand-to-product correlation in our original disclosure regarding ligand $\mathbf{L_B}$.[6] Recently, Hoveyda used our (*S*)-(–)-**3** correlation in a communication using $\mathbf{L_C}$ attaining **3** in very high enantiomeric excess.[7] For all of these reasons we felt it was appropriate to explicitly check the required correlations again and this short note gives the outcome of this study.

Reaction of **1** with $AlMe_3$, utilising 5.5 mol% (*S*)-$\mathbf{L_A}$ under our improved conditions,[8] afforded a 53% isolated yield of (–)-**2** in 85% e.e. by chiral GC. Dramatically improved conversion of (–)-**2** to (–)-**3** could be attained by treatment with Na_2CO_4/CF_3CO_2H followed by hydrolysis of the trifluroacetate/acetate mixture.[9] The specific rotation of this catalyst derived (–)-**4** [–14.8 (*c* 0.31 MeOH)] was comparable to the published value for (*S*)-(–)-**4** [–13.1 (*c* 1.15 in $CHCl_3$)] and similar to that for the related compound (*S*)-(–)-**6**

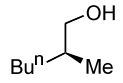


Scheme 1. Methyl and ethyl addition products, from asymmetric conjugate additions to (*E*)-**1**, and their Baeyer–Villiger derived alcohols. All $[\alpha]_D$ values were obtained in MeOH at *c* 0.31.

* Corresponding author. Tel.: +44-115-951-3541; fax: +44-115-951-3564; e-mail: simon.woodward@nottingham.ac.uk

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00574-8

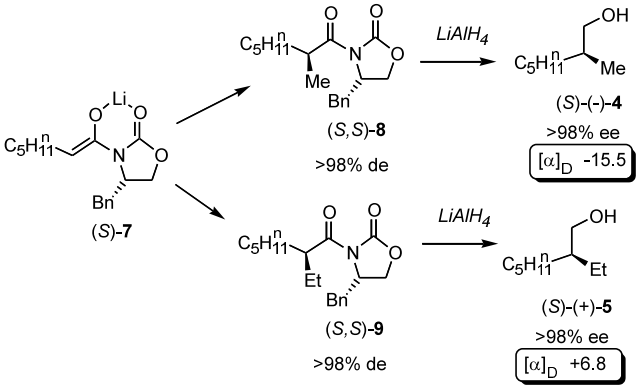
[−14.2 (*c* 0.31, MeOH)].[10] Treatment of **1** with $ZnEt_2$ and (*R*)-$\mathbf{L_B}$ (20 mol%) under the literature conditions yielded (−)-**3** [−2.4 (*c* 0.31 MeOH)] with the chiral GC elution properties expected for the (*S*) enantiomer. However, Baeyer–Villiger degradation using percarbonate/TFA yielded **5** with a positive rotation (Scheme 1). This finding necessitates independent synthesis of (*S*)-**5** to make sure this is the (+) antipode and that a stereochemical misassignment has not occurred.



(*S*)-(-)-**6**
>98% ee
$[\alpha]_D$ -14.2 (*c* 0.31, MeOH)

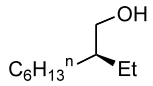
2. Independent synthesis

Ample literature precedent[11] shows that alkylations of the lithium enolate (*S*)-**7** occur exclusively from the top face, yielding, in our cases, the required (*S*) centre after alkylation with methyl or ethyl iodide (Scheme 2).



Scheme 2. Alternative preparations of (*S*)-**4** and (*S*)-**5** using Evans' auxiliary chemistry. Enolate (*S*)-**7** was alkylated with RI (R = Me, Et); $[\alpha]_D$ values are under (*c* 0.31, MeOH) conditions.

In our hands, the yield of (*S*,*S*)-**9** was unexpectedly low (21%) but the compound was isolated in a chemically and stereochemically pure form (the mass balance of the reaction was accounted for by the proton quench product of (*S*)-**7**). The yields of reactions of (*S*)-**7** are known to be dependent on the electrophile used and are often below 40% for reactions of lithium enolates with EtI. Treatment of (*S*,*S*)-**8** or (*S*,*S*)-**9** with $LiAlH_4$ leads to clean formation of the required alcohols for comparison purposes and indicates the correctness of our original proposal.[2] The only spectroscopic feature of note is that the α-hydroxylic protons of (*S*)-**5** are highly second order and appear as an apparent doublet in the ^1H NMR spectrum at 400 MHz ($CDCl_3$). As added proof, Normant reported a positive rotation for (*S*)-**10** in carbometallation studies.[12] In a final comparison we subjected (*E*)-**1** to Hoveyda's conditions[7] and obtained, under unoptimised conditions using $ZnEt_2$, (*R*)-(+)-**3** in 83% e.e. the major antipode eluting second on our GC column. This sample when subjected to Baeyer–Villiger degradation with Na_2CO_4/TFA yielded (*R*)-**5** with a negative optical rotation in agreement with our own studies.



(*S*)-(+)-**10**
74% ee
$[\alpha]_D$ +2.4 (*c* 2.0, $CHCl_3$)

3. Conclusion

We have demonstrated explicitly that all stereochemical assignments made for the methyl and ethyl addition products derived from (*E*)-**1** are correct. However, it is apparent that the optical rotations of the alkyl addition products of (*E*)-$R^1CH{=}CH(COR^2)$ enone (R^1, R^2 = alkyl) and their Baeyer–Villiger oxidation products are small and subject to reversal in an unpredictable manner.[13] Therefore, stereochemical assignments based only on comparison of specific rotation data will be inappropriate in some cases.

4. Experimental

The general experimental setup has been described before.[1–3] Optical rotations were measured on a JASCO DIP-370 instrument. Key specific rotations in units of 10^{-1} deg. cm^2 g^{-1} (*c* in g/100 cm^3) are reported in Schemes 1 and 2.

4.1. Asymmetric conjugate additions

4.1.1. (*S*)-(−)-4-Methylnonan-2-one, (*S*)-(−)-2. To a stirred 0.028 M solution of (*S*)-$\mathbf{L_A}$ (35 mg, 0.098 mmol) and $[Cu(MeCN)_4]BF_4$ (28 mg, 0.089 mmol) in absolute THF at −45°C was simultaneously added (*E*)-3-nonen-2-one in THF (250 mg, 1.783 mmol, 0.72 ml) and a solution of $AlMe_3$ in THF (1.40 M, 0.72 ml) with a syringe pump over a period of 20 min. After stirring for 16 h at −45°C, the reaction solution was diluted with Et_2O and quenched with aqueous 1 M HCl. The aqueous layer was extracted four times with Et_2O, washed twice with brine, dried over $MgSO_4$ and chromatographed on silica gel (Et_2O:petrol 1:9) to afford **2** (148 mg, 0.947 mmol) as a clear oil with the expected spectroscopic data[1,7] (e.e. 85%, *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin[5]).

4.1.2. (*S*)-(−)-4-Ethylnonan-2-one, (*S*)-(−)-3. To a 0.0028 M solution of ligand (*R*)-$\mathbf{L_B}$ (66 mg, 0.178 mmol, 10 mol%) and $[Cu(MeCN)_4]BF_4$ (28 mg, 0.098 mmol, 5 mol%) in anhydrous anaerobic THF were added simultaneously a solution of $ZnEt_2$ in THF (1.0 M, 3.92 mL, 3.92 mmol, 2.2 eq.) and (*E*)-3-nonen-2-one in THF (0.72 M solution, 250 mg (1.783 mmol) over a period of 20 min to the chilled reaction solution

(−20°C). After stirring for a further 20 min the reaction mixture was treated as above to afford (*S*)-(−)-4-ethylnonan-2-one **3** (259 mg, 1.52 mmol, 85%) as a pale yellow oil with the expected spectroscopic properties[3,7] (62% e.e., *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin[5]).

4.2. Baeyer–Villiger oxidations

4.2.1. (*S*)-2-Methylheptanol, (*S*)-(−)-4. To a stirred solution of (*S*)-(−)-4-methylnonan-2-one **2** (112 mg, 0.717 mmol) in TFA (1.0 mL) at 0°C were added sodium percarbonate (225 mg, 1.434 mmol) in small portions. After stirring for 16 h at room temperature, the reaction mixture was diluted with MeOH/H_2O 9:1 solution (5 mL), cooled at 0°C, and treated with an excess of KOH. The reaction was complete in 15 min (TLC). The aqueous layer was diluted with Et_2O and water, extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$, then evaporated. Chromatography with Et_2O:petrol 1:10 afforded the alcohol (82 mg, 0.63 mmol, 88%) as a pale yellow liquid. R_f (1:2 Et_2O:petrol) 0.21; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.52 (dd, $J=10.4$ and 5.7 Hz, 1H), 3.43 (dd, $J=10.4$ and 5.7 Hz, 1H), 1.61 (m, 1H), 1.44–1.20 (m, 8H), 0.92 (t, $J=6.7$ Hz, 3H), 0.89 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 68.4, 35.8, 33.1, 32.1, 26.6, 22.6, 16.55, 14.05; IR (neat): 3332, 2925, 1465, 1378, 1033 cm^{-1}, HRMS (EI): calcd for C_8H_{16}: 112.12520 (M^+-H_2O), found: 112.12548; MS (EI): 112 (M^+-H_2O, 8%), 98 (9), 70 (52), 57 (100).

4.2.2. (*S*)-(+)-2-Ethylheptanol, (*S*)-(+)-5. In the same manner as described for the synthesis of **4**, 347 mg (2.04 mmol) of 4-(*S*)-(−)-ethylnonan-2-one **3** reacted to yield 215 mg (1.49 mmol) of (*S*)-(+)-2-ethylheptanol **5** in 73% yield as a pale yellow liquid. R_f (1:2 Et_2O:petrol) 0.23; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.56 (apparent d, $J=5.2$ Hz, 2H), 1.47–1.28 (m, 11H), 0.94–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 65.3, 42.0, 32.3, 30.4, 26.6, 23.4, 22.6, 14.1, 11.1; IR (neat): 3332, 2926, 1463, 1379, 1040 cm^{-1}; HRMS (EI): calcd for C_9H_{18}: 126.14085 (M^+-H_2O), found: 126.14057; MS (EI): 126 (M^+-H_2O, 18%), 112 (14), 97 (52), 71 (90), 57 (100).

4.3. Alkylations of Evans' auxiliary

4.3.1. (*S*,*S*)-(+)-4-Benzyl-3-(-2-methylheptanoyl)oxazolidin-2-one, (*S*,*S*)-8. To a stirred solution of *N*,*N*-diisopropylamine (0.40 mL, 2.90 mmol) in absolute THF (7 mL) at −78°C was added a 2.5 M solution of *n*-BuLi in hexanes (1.2 mL, 2.90 mmol). After stirring for 15 min at −78°C, heptanoyl-Evans' auxiliary[11] (700 mg, 2.42 mmol) in absolute THF (3 mL) was added dropwise followed, after 30 min, by MeI (0.18 mL, 2.90 mmol). The reaction mixture was stirred overnight at room temperature, quenched with 0.1 M aqueous HCl solution, extracted four times with Et_2O. The extract was washed once with brine, and dried over $MgSO_4$. Flash chromatography (Et_2O:petrol, 1:5) afforded (*S*,*S*)-**8** (472 mg, 1.56 mmol, 64%) as a colourless oil. R_f (1:2 Et_2O:petrol) 0.27; $[\alpha]_D=+140.0$ (*c* 0.30, Et_2O); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33 (ddd, $J=7.6$, 7.2 and 1.5 Hz, 2H), 7.28 (dt, $J=7.2$ and 1.5 Hz, 1H), 7.22 (dd, $J=7.6$ and 1.5 Hz, 2H), 4.68 (ddt, $J=7.3$, 7.3 and 3.2 Hz, 1H), 4.17 (dd, $J=9.0$ and 7.4 Hz, 2H), 3.71 (br, 1H), 3.27 (dd, $J=13.3$ and 10.1 Hz, 1H), 2.77 (dd, $J=13.3$ and 9.6 Hz, 1H), 1.43–1.36 (m, 1H), 1.35–1.25 (m, 6H), 1.22 (d, $J=6.8$ Hz, 3H), 0.88 (t, $J=6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.3, 153.0, 135.3, 129.4, 128.85, 127.25, 65.9, 55.3, 37.8, 37.6, 33.3, 31.75, 26.85, 22.45, 17.3, 14.0; IR (neat): 1782, 1698, 1605, 1497, 1455, 1385, 1211, 1099, 702 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{25}NO_3$: 303.18344 (M^+), found: 303.18324; MS (EI): 303 (M^+, 5%), 212 (14), 178 (7), 127 (57), 99 (21), 91 (14), 57 (100).

4.3.2. (*S*,*S*)-(+)-4-Benzyl-3-(-2-ethylheptanoyl)oxazolidin-2-one, (*S*,*S*)-9. Under the same conditions as described above heptanoyl-Evans' auxiliary[11] was allowed to react with iodoethane to afford (*S*,*S*)-**9** in 21% yield as a colourless oil. R_f (1:2 Et_2O:petrol) 0.32; $[\alpha]_D=+126.7$ (*c* 0.30, Et_2O); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34 (dd, $J=7.5$ and 7.1 Hz, 2H), 7.28 (dt, $J=7.1$ and 1.5 Hz, 1H), 7.24 (dd, $J=7.5$ and 1.5 Hz, 2H), 4.71(ddt, $J=9.1$, 9.1 and 6.1 Hz, 1H), 4.17 (dd, $J=9.1$ and 6.1 Hz, 2H), 3.74 (dt, $J=7.7$ and 5.7 Hz, 1H), 3.35 (dd, $J=13.3$ and 10.0 Hz, 1H), 2.71 (dd, $J=13.2$ and 10.0 Hz, 1H), 1.83–1.42 (m, 4H), 1.34–1.28 (m-br, 6H), 0.97 (t, $J=7.4$ Hz, 3H), 0.88 (t, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.8, 153.1, 135.4, 129.4, 128.9, 127.3, 65.85, 55.5, 44.05, 38.1, 31.9, 31.4, 27.0, 25.4, 22.5, 14.0, 11.4; IR (neat): 1778, 1697, 1605, 1497, 1455, 1388, 1235, 1098, 702 cm^{-1}; HRMS (EI): calcd for $C_{19}H_{27}NO_3$: 317.19910 (M^+), found: 317.20003; MS (EI): 317 (M^+, 29%), 247 (8), 226 (15), 178 (13), 141 (100), 91 (18), 82 (30), 71 (43), 57 (51).

4.4. Reduction of Evans' auxiliary products

To a suspension of $LiAlH_4$ (120 mg, 3.16 mmol) in absolute THF (5 ml) at 0°C was added (*S*,*S*)-**8** (240 mg, 0.79 mmol) in THF (1 mL). After stirring for 30 min, the reaction mixture was diluted with Et_2O and carefully quenched with THF/H_2O and H_2O until a white precipitate appears. The Et_2O/THF solution is then decanted and the flask washed several times with Et_2O. Drying over $MgSO_4$ and chromatography on silica gel with Et_2O:petrol 1:2 as eluent gave (*S*)-(−)-2-methylheptanol (*S*)-(−)-**4** (86 mg, 0.66 mmol, 83%). In the same manner, (*S*)-(+)-2-ethylheptanol (*S*)-(+)-**5** was obtained in 81% yield. The spectroscopic properties of these materials were both identical to those derived by the Baeyer–Villiger oxidation/hydrolysis procedure.

Acknowledgements

Support from EPSRC (GR/N37339), COST-D12 (0022/99) and COST-D24 (0003/01) is gratefully acknowledged. We thank Professor Amir H. Hoveyda and Sylvia J. Degrado for discussions and for supplying a sample of $\mathbf{L_c}$.

References

1. Bennett, S. M. N.; Brown, S. M.; Cunningham, A.; Dennis, M. R.; Muxworthy, J. P.; Oakley, M. A.; Woodward, S. *Tetrahedron* **2000**, *56*, 2847–2855.
2. Börner, C.; König, W. A.; Woodward, S. *Tetradedron Lett*. **2001**, *42*, 327–329.
3. Börner, C.; Dennis, M. R.; Sinn, E.; Woodward, S. *Eur. J. Org. Chem*. **2001**, 2435–2446.
4. (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett*. **1989**, *30*, 5603–5606; (b) Högberg, H.-E.; Hendenström, E.; Fägerhag, J. *J. Org. Chem*. **1992**, *57*, 2052–2059.
5. König, W. A.; Icheln, D.; Runge, T.; Pforr, I.; Krebs, A. *J. High Resolut. Chromatogr*. **1990**, *13*, 702–707.
6. See footnote 17 in Ref. 3: (*R*)-$\mathbf{L_B}$ gives (*S*)-(−)-**3**; this was accidentally inverted in Ref. 1 (Table 4, entries 18 and 19).
7. Mizututani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 779–781.
8. Fraser, P. K.; Woodward, S., unpublished results.
9. Olah, G. A.; Wang, Q.; Trivedi, N. J.; Prakash, G. K. S. *Synthesis* **1991**, 739.
10. Grover, P.; Cecicco, C. P. *J. Org. Chem*. **1996**, *61*, 3534–3541.
11. (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737–1739; (b) For a review, see: Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835–837.
12. Noraikian, S.; Baudry, M.; Normant, J. F. *Tetrahedron Lett*. **2000**, *41*, 6575–6578.
13. For example, use of (*S*)-$\mathbf{L_A}$ gives (−)-**2** similarly the (−) antipode of CyCH(Me)CH_2COMe is also isolated by use of (*S*)-$\mathbf{L_A}$ and CyCH=CHCOMe. However, enone Pr^iCH=CHCOMe gives the (+) isomer under the same conditions. See: Fraser, P. K.; Woodward, S., unpublished results.