Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1913–1918

(1*S*,2*S*)-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene: a new chiral auxiliary for asymmetric Reformatsky reactions

Fulvia Orsini,* Guido Sello, Angelo Maria Manzo and Elvira Maria Lucci

Dipartimento di Chimica Organica e Industriale, Via Venezian 21, 20133 Milano, Italy

Received 19 January 2005; revised 14 April 2005; accepted 15 April 2005

Abstract—(1*S*,2*S*)-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene, synthesized via a chemoenzymatic approach from naphthalene, has been successfully used as a chiral auxiliary in Reformatsky-type reactions between the corresponding α-bromoacyloxazolidinone and carbonyl compounds.

1. Introduction

It is widely recognized that chiral amino alcohols are versatile reagents for the preparation of enantiopure compounds. For this purpose they can be used directly or derivatized to give, for example, chiral oxazolidinones, acetonides, hydroxyesters and hydroxyamides.[1]

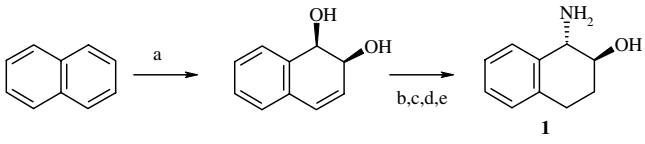
Many chiral amino alcohols have been used as backbones of chiral oxazolidinones. The latter have been widely used as auxiliaries for a variety of asymmetric transformations,[1] such as *C*-alkylations,[2] acylations,[3] α-amination, aldol reactions,[4] Michael additions[5] and Diels–Alder reactions.[6] The methodologies have been applied to the preparation of a variety of natural products[7] as well as biologically and medicinally important compounds. Some oxazolidinones also possess biological activity on their own. The frequent use of oxazolidin-2-ones has prompted the investigation of several methodologies of synthesis[8] and acylation[9] of these type of molecules. *N*-Acyloxazolidinones are among the most versatile chiral auxiliary systems, due to their ability to form rigid chelates with metal ions, especially in the presence of a bulk substituent in the 4-position.

Reformatsky-type reactions between α-bromoacyloxazolidinones and carbonyl compounds have been successfully performed with different metals and applied to the construction of medicinally important compounds. Such an example is the synthesis of the dolaproin unit of Dolastin,[10] an anti-tumour agent, via a Co(0)-mediated Reformatsky-type protocol developed in our laboratory.[11] Another metal, which has proven quite useful is samarium (used as SmI_2) for its remarkable stereoselectivity, achieved through chelation control of the samarium intermediate in the transition state.[12]

It is also well known that amide-containing chiral auxiliaries often require harsh conditions in order to remove them, thus limiting their usefulness and general applicability. However it has been demonstrated that ester derivatives of *cis*-1-*p*-tolylsulfonamido-2-indanol can be successfully used in asymmetric synthesis.[13]

Herein, we report some results concerning the use of (1*S*,2*S*)-1-amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene **1** (Scheme 1), obtained via a chemoenzymatic approach from the inexpensive and convenient naphthalene (Scheme 1),[14] as a chiral auxiliary in Reformatsky-type reactions.

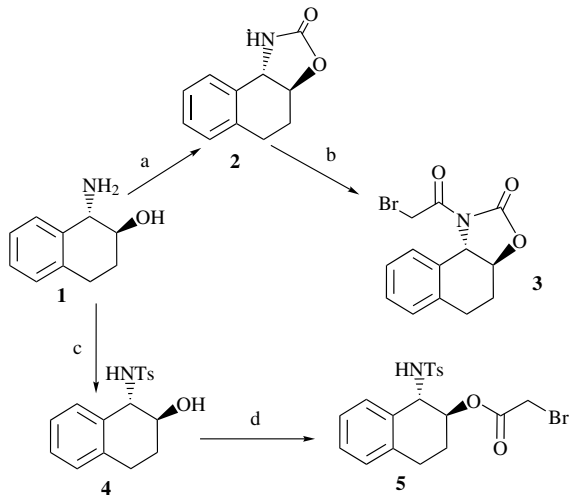
For this purpose, two different strategies were followed: in the first, **1** was first converted to the chiral α-bromoacyloxazolidinone **3**, while in the second, **1** was



Scheme 1. Reagents and conditions: (a) *Escherichia coli* JM109$^{(pVL13+pMS13)}$; (b) H_2, Pd/C, MeOH; (c) triphosgene, triethylamine, CH_2Cl_2, 0 °C; (d) NaN_3, DMF, 110 °C; (e) H_2, Pd/C, MeOH, 25 °C.

* Corresponding author. Tel.: +39 02 50314111; fax: +39 02 50314106; e-mail: fulvia.orsini@unimi.it

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.04.008



Scheme 2. Reagents and conditions: (a) Triphosgene, triethylamine, CH_2Cl_2, 0 °C; (b) BuLi, THF, −78 °C; bromoacetyl chloride, triethylamine, CH_2Cl_2, 25 °C; (c) tosyl chloride, 2,4-di-methyl aminopyridine, CH_2Cl_2, 25 °C; (d) bromoacetyl chloride, triethylamine, CH_2Cl_2, 25 °C.

converted to the 1-*p*-tolylsulfonamido-2-(α-bromoacyloxy)-derivative **5** (Scheme 2).

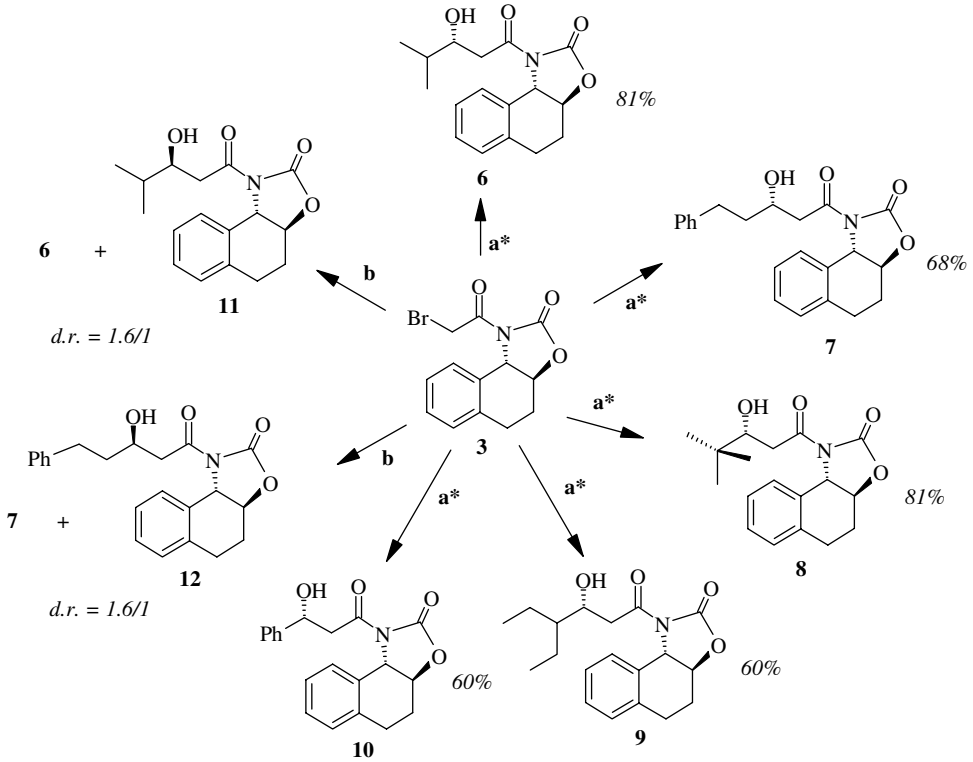
2. Results and discussion

Amino alcohol **1** was synthesized in a few steps, in good total yields (80%) and under mild neutral conditions from the *cis*-diol obtained by bioconversion of naphthalene.[14] Reaction with triphosgene in methylene chloride in the presence of triethylamine at 0 °C afforded oxazolidinone **2** in 87% yield. *N*-Bromoacyloxazolidinone **3** was readily accessible in a reasonable yield (70%) by reaction of the auxiliary **2** with butyllithium in toluene at low temperature, followed by addition of bromoacetyl chloride. Bromoacetyl bromide was also tested, but gave lower yields and unidentified side products.

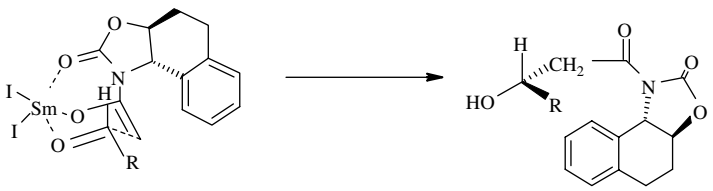
We first tested the reaction of isobutyraldehyde with chiral bromoacyloxazolidinone **3** at room temperature. Unfortunately, the diastereoselectivity of the reaction proved unsatisfactory, giving both diastereomers in a 1.6/1 ratio. The reaction was then carried out at −78 °C with only one diastereoisomer isolated in about 80% yield. Other aldehydes were then used and the results summarized in Scheme 3. The yields were in general from reasonable to good[15,16] and one diastereoisomer was isolated at low temperature.

The lowest yields were obtained with benzaldehyde, which are more inclined to give pinacol coupling: a problem that can be minimized by the stepwise addition of organic reagents (bromoacyloxazolidinone first, followed by benzaldehyde).

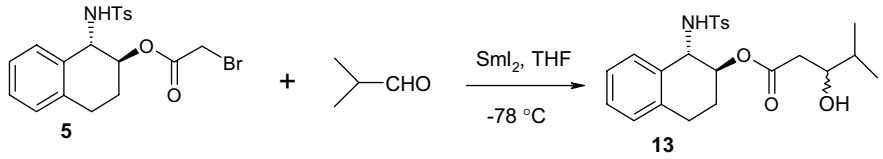
The depicted stereochemistry has been suggested assuming that the stereochemistry of the Reformatsky adduct can be determined by a chelate transition structure involving a samarium enolate with the samarium atom coordinated to the oxazolidinone carbonyl, as verified in other cases[17] (Scheme 4). This assumption has been experimentally verified in cases **6**, **8** and **10**. Cleavage



Scheme 3. Reagents and conditions: (a) Bromoacyloxazolidinone (1 equiv), carbonyl compound, SmI_2 (2 equiv), THF, −78 °C; (b) bromoacyloxazolidinone (1 equiv), carbonyl compound, SmI_2 (2 equiv), THF, 25 °C (*—dr >99/1).



Scheme 4.



Scheme 5.

of the chiral auxiliary with lithium hydroxide[18] afforded indeed the corresponding (*R*)-β-hydroxy acids.[19]

The second devised strategy involved the conversion of the aminoalcohol **1** into the *p*-tolylsulfonamido derivative **5** in two steps with 50% total yield: treatment with *p*-toluenesulfonyl chloride in dichloromethane in the presence of 2,4-dimethylaminopyridine afforded derivative **4**, which was subsequently reacted with α-bromoacetyl chloride in dichloromethane in the presence of triethylamine. The Sm(II)-mediated Reformatsky-type reaction with isobutyraldehyde, performed at −78 °C, afforded, however, a diastereoisomeric mixture of aldols in almost equimolar amounts (Scheme 5).

3. Conclusion

In conclusion, (1*S*,2*S*)-1-amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene, previously converted to the corresponding α-bromoacyloxazolidinone, can be efficiently used as a chiral auxiliary in Reformatsky-type reactions to afford β-hydroxy acids.

4. Experimental

4.1. General

Reagent grade tetrahydrofuran was refluxed on $LiAlH_4$ and distilled. Reagent grade dichloromethane was heated under reflux over P_2O_5 and distilled. Triethylamine was refluxed on calcium hydride and distilled. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) were recorded at 300 MHz in $CDCl_3$ solutions. Mass spectra were recorded with a VG7070 E9 instrument. Melting points were determined with a capillary apparatus and are uncorrected.

4.2. Synthesis of the oxazolidinone 2

To a solution of amino alcohol **1** (1.43 g, 8.7 mmol) and freshly distilled triethylamine (1.8 mL) in dry methylene chloride (18 mL) was added a solution of triphosgene (0.89 g, 3 mmol) in methylene chloride, dropwise in about 1 h at 0–10 °C. The reaction was monitored by thin layer chromatography (SiO_2, chloroform–methanol–isopropylamine 9.5:0.25:0.25). After 2 h, methanol (3 mL) and water (5 mL) were added to the reaction mixture, which was vigorously stirred for an additional 30 min, concentrated under reduced pressure, after which was added 10 mL of water and stirred for a further 10 min. The suspension was filtered on a buckner, washed with 1 M hydrochloric acid (0.2 mL) and water (0.8 mL), to afford pure oxazolidinone **2** in 87.5% total yield (1.38 g, 7.54 mmol).

4.2.1. (4*S*,5*S*)-Tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 2. Colourless crystals, mp = 157 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +14.0$ (*c* 10, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.14 (1H, m), 2.45 (1H, m), 3.08 (1H, ddd, $J = 18.0$, 18.0, 8.0 Hz), 3.18 (1H, ddd, $J = 18.0$, 9.0, 3.0 Hz), 4.20 (1H, ddd, $J = 11.0$, 11.0, 5.0 Hz), 4.6 (1H, d, $J = 11.0$ Hz), 6.6 (1H, s), 7.0–7.3 (4H); ^{13}C NMR ($CDCl_3$): 23.62 (t), 26.39 (t), 60.30 (d), 81.17 (d), 122.89 (d), 126.39 (d), 127.67 (d), 128.70 (d), 133.67 (s), 134.71 (s), 161.81 (s); EI MS, *m*/*z* (%): 189 (59) (M^+), 161 (100) (M^+-CO), 144 (39) (M^+-COO), 129 (29) ($M^+-NHCOO$). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.84; H, 5.82. Found: C, 69.63; H, 5.88.

4.3. Synthesis of the α-bromoacetyl-2-oxazolidinone 3

To a solution of oxazolidinone **2** (1.382 g, 7.55 mmol) in dry tetrahydrofuran (12 mL), at −78 °C, a solution of butyllithium (1.6 M in hexane, 5.2 mL) was added dropwise in about 20 min. The resulting solution was stirred at −78 °C for an additional 30 min. α-Bromoacetyl chloride (0.340 mL) in tetrahydrofuran (2 mL) was added dropwise in about 20 min. The reaction mixture was allowed to reach room temperature in about 1 h. A solution of saturated monohydrogenphosphate (5 mL) was then added and the water phase extracted (3×10 mL) with ethylacetate. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material

was chromatographed on silica gel (eluting with ethylacetate/*n*-hexane 2:8) and afforded α-bromoacetyl-2-oxazolidinone **3** (70%) and starting oxazolidinone (20%).

4.3.1. *N*-(α-Bromoacetyl)-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 3. Colourless crystals, mp = 126 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +272$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.08 (1H, m), 2.40 (1H, m), 3.02 (1H, ddd, *J* = 14.3, 9.2, 3.7 Hz), 3.18 (1H, ddd, *J* = 14.3, 9.1, 4.0 Hz), 4.10 (1H, ddd, *J* = 11.2, 11.2, 8.0 Hz), 4.42 (1H, d, *J* = 12 Hz), 4.86 (1H, d, *J* = 12 Hz), 4.88 (1H, d, *J* = 11.2 Hz), 7.0 (1H, dd, *J* = 5.5, 1.8 Hz), 7.15–7.25 (3H). ^{13}C NMR ($CDCl_3$): 22.12 (t), 25.69 (t), 28.43 (t), 61.40 (d), 78.79 (d), 123.21 (d), 126.68 (d), 127.77 (d), 128.52 (d), 133.84 (s), 134.59 (s), 154.70 (s), 169.54 (s); EI MS, *m*/*z* (%): 311–309 (19) (M^+), 230 (76) (M^+-Br), 188 (82) (M^+-BrCH_2CO), 144 (29) ($188-CO_2$), 130 (100) ($C_{10}H_{10}$). Anal. Calcd for $C_{13}H_{12}BrNO_3$: C, 50.32; H, 3.87. Found: C, 50.26; H, 3.87.

4.4. Synthesis of β-hydroxyacyloxazolidinones 6–10

4.4.1. Typical procedure at −78 °C. To a tetrahydrofuran solution of samarium iodide (0.1 M, 1.25 mmol), the bromoacyloxazolidinone **3** (0.175 g, 0.55 mmol) and the aldehyde (0.55 mmol) in dry tetrahydrofuran (1 mL) were added dropwise (30 min) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min and the colour of the solution turned from deep blue to yellow.[14] A diluted HCl solution (0.1 N, 9 mL) was then added and the aqueous phase was extracted three times with ethylacetate (3 × 5 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure to afford the crude material, which was purified by column chromatography (SiO_2; eluting with ethylacetate/*n*-hexane).

4.4.2. *N*-[(3*R*)-3-Hydroxy-4-methyl-pentanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 6. Yield 81%, colourless crystals, mp = 145–146 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +208.4$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.02 (6H, d, *J* = 6.5 Hz), 1.81 (1H, mt, *J* = 6.5 Hz), 2.07 (1H, dddd, *J* = 11.0, 11.0, 10.8, 3.6 Hz), 2.37 (1H, m), 3.0 (1H, ddd, *J* = 17.5, 9.1, 3.6 Hz), 3.11 (1H, dd, *J* = 16.2, 6.0 Hz), 3.16 (1H, ddd, *J* = 17.5, 10.8, 5.4 Hz), 3.32 (1H, dd, *J* = 16.2, 2.2 Hz), 3.97 (1H, m), 4.06 (1H, m), 4.85 (1H, d, *J* = 11.5), 7.05–7.42 (4H); ^{13}C NMR ($CDCl_3$): 13.44 (q), 17.68 (q), 18.46 (d), 22.06 (t), 25.70 (t), 33.75 (d), 41.43 (t), 73.73 (d), 78.29 (d), 126.53 (d), 126.54 (d), 127.63 (d), 128.46 (d), 133.95 (s), 135.17 (s), 155.33 (s), 176.43 (s); MS *m*/*z* (%): 285 (1) (M^+-H_2O), 260 (10) ($M^+-(CH_3)_2CH$), 216 (92) ($M^+-(CH_3)_2CHCH(OH)CH_2$), 188 (21) ($216-CO$), 172 (11) ($216-CO_2$), 130 (100) ($C_{10}H_{10}$). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93. Found: C, 67.63; H, 6.98.

4.4.3. *N*-[(3*S*)-3-Hydroxy-5-phenyl-pentanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 7. Yield 68%, colourless crystals, mp = 155–156 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +271.1$ (*c* 1.66, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.85–1.95 (2H, m), 2.05 (1H, m), 2.4 (1H, m), 2.7–2.9 (2H, m), 2.98 (1H, ddd, *J* = 15.4, 8.8, 4.4 Hz), 3.18 (1H, ddd, *J* = 15.4, 6.6, 4.9 Hz), 3.25 (2H, *J* = 6.2 Hz), 4.02 (1H, ddd, *J* = 11.1, 11.0, 8.4 Hz), 4.25 (1H, m), 4.83 (1H, d, *J* = 11.1 Hz), 7.01–7.3 (9H); ^{13}C NMR ($CDCl_3$): 22.29 (t), 25.89 (t), 29.88 (t), 38.72 (t), 44.20 (d), 61.52 (d), 68.18 (d), 123.62 (d), 126.10 (d), 126.72 (d), 127.02 (d), 127.88 (d), 128.13 (d), 2 × 128.64 (d), 128.68 (d), 134.13 (s), 135.34 (s), 141.90 (s), 155.41 (s), 176.20 (s); MS, *m*/*z* (%): 365 (1) (M^+), 347 (52) (M^+-H_2O), 130 (100) ($C_{10}H_{10}$), 91 (100) ($C_6H_5CH_2$). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.33; H, 6.30. Found: C, 72.63; H, 6.38.

4.4.4. *N*-[(3*R*)-3-Hydroxy-4,4-dimethyl-pentanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 8. Yield 81%, mp = 116–118 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +290.3$ (*c* 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.02 (9H, s), 2.06 (1H, dddd, *J* = 11.0, 11.0, 10.8, 4.3 Hz), 2.36 (1H, m), 2.98 (1H, ddd, *J* = 15.2, 8.7, 4.3 Hz), 3.04 (1H, dd, *J* = 13.6, 11.1 Hz), 3.15 (1H, ddd, *J* = 15.2, 10.8, 5.4 Hz), 3.36 (1H, dd, *J* = 13.6, 3.0 Hz), 3.88 (1H, dd, *J* = 11.1, 3.0 Hz), 4.03 (1H, ddd, *J* = 11.0, 10.8, 6.5 Hz), 4.84 (1H, d, *J* = 10.8 Hz), 7.05–7.15 (4H); ^{13}C NMR ($CDCl_3$): δ 22.12 (t), 25.38 (t), 3 × 25.56 (q), 34.89 (s), 39.57 (t), 61.29 (d), 76.59 (d), 78.27 (d), 123.50 (d), 126.58 (d), 127.62 (d), 128.42 (d), 133.96 (s), 135.23 (s), 155.35 (s), 176.63 (s); MS *m*/*z* (%): 299 (1) (M^+-H_2O), 273 (4) (M^+-CO_2), 260 (63) ($M^+-(CH_3)_3C$), 216 (32) ($M^+-(CH_3)_3CCH(OH)CH_2$), 130 (100) ($C_{10}H_{10}$). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.14; H, 7.26. Found: C, 68.45; H, 7.28.

4.4.5. *N*-[(3*R*)-3-Hydroxy-4-ethyl-hexanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 9. Yield 60%, mp = 92–93 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +309.3$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.04 (3H, d, *J* = 7.5 Hz), 1.04 (3H, d, *J* = 7.5 Hz), 1.3–1.6 (5H, m), 2.05 (1H, dddd, *J* = 10.0, 10.0, 10.0, 4.0 Hz), 2.35 (2H, m), 2.98 (1H, ddd, *J* = 15.0, 10.0, 4.0 Hz), 3.15 (1H, dd, *J* = 15.0, 10.0, 4.4 Hz), 3.15 and 3.25 (2H, ABX system, J_{AB} = 15.0 Hz, J_{AX} = 5.0 Hz, J_{BX} = 2.5 Hz), 4.0 (1H, ddd, *J* = 10.0, 10.0, 6.0 Hz), 4.23 (1H, ddd, *J* = 10.0, 5.0, 2.5 Hz), 4.83 (1H, d, *J* = 10.0 Hz), 7.1–7.3 (4H); ^{13}C NMR: 2 × 11.82 (q), 20.86 (t), 21.32 (t), 21.78 (t), 21.99 (t), 25.48 (t), 46.75 (d), 61.22 (d), 70.12 (d), 78.20 (d), 123.73 (d), 126.76 (d), 127.04 (d), 128.35 (d), 133.99 (s), 135.20 (s), 155.31 (s), 176.45 (s); MS, *m*/*z* (%): 313 (5) (M^+-H_2O), 260 (54) ($331-CH_3CH_2CHCH_2CH_3$), 216 (30) ($260-CH(OH)CH_2$), 172 (7) ($216-CO_2$), 130 (100) ($C_{10}H_{10}$). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.88; H, 7.55. Found: C, 68.55; H, 7.67.

4.4.6. *N*-[(3*R*)-3-Hydroxy-3-phenyl-pentanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 10. Yield 60%, mp = 156–157 °C (ethylacetate/*n*-hexane); $[\alpha]_D = +284.0$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.05 (1H, dddd, *J* = 10.0, 10.0, 10.0, 4.8 Hz), 2.48 (1H, ddd, *J* = 15.0, 10.0, 4.8 Hz), 3.15 (1H, ddd, *J* = 17.5, 10.0, 5.0 Hz), 3.28 (1H, m), 3.48 and 3.55 (2H, ABX system, J_{AB} = 15.0 Hz, J_{AX} = 9.0 Hz, J_{BX} = 5.0 Hz), 4.02 (1H, ddd, *J* = 10.0, 10.0, 5.3 Hz), 4.85 (1H, d, *J* = 10.0 Hz), 5.35 (1H, dd, *J* = 9.0, 5.0 Hz), 7.01–7.25 (9H); ^{13}C

NMR ($CDCl_3$): 21.50 (t), 24.14 (t), 46.04 (t), 61.18 (d), 71.03 (d), 78.32 (d), 123.38 (d), 2 × 125.83 (d), 126.44 (d), 127.54 (d), 127.88 (d), 128.36 (d), 2 × 128.50 (d), 133.89 (s), 135.05 (s), 142.81 (s), 155.20 (s), 174.88; MS, *m/z* (%): 337 (80) (M^+), 231 (16) ($M^+-PhCHO$), 187 (33) ($231-CO_2$), 130 (100) ($C_{10}H_{10}$). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.22; H, 5.64. Found: C, 71.35; H, 5.68.

4.5. Synthesis of β-hydroxyacyloxazolidinones 6, 7, 11 and 12

4.5.1. Typical procedure at room temperature. To a tetrahydrofuran solution of samarium iodide (0.1 M, 1.25 mmol), bromoacyloxazolidinone **3** (0.175 g, 0.55 mmol) and isobutyraldehyde (0.175 g, 0.55 mmol) in tetrahydrofuran (1 mL) were added dropwise (30 min) at room temperature. The reaction was monitored in thin layer chromatography (SiO_2; eluting with ethylacetate/*n*-hexane 3:7), stirred at room temperature for an additional 90 min, and then worked up as described above for the reactions performed at low temperature. The crude material was purified by column chromatography (SiO_2; eluting with ethylacetate/*n*-hexane 3:7) and afforded the diastereoisomeric aldols **6** and **11** in 1.6:1 ratio.

4.5.2. *N*-[(3*S*)-3-Hydroxy-5-methyl-pentanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 11. $[\alpha]_D$ = +150.5 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.0 (3H, d, J = 5.6 Hz), 1.02 (3H, d, J = 5.6 Hz), 1.82 (1H, m), 2.06 (1H, m), 2.38 (1H, m), 3.0 (1H, ddd, J = 16.0, 10.0, 2.5 Hz), 3.08–3.35 (2H, dd, J = 15.0, 1.5, 10.0 Hz), 3.18 (1H, ddd, J = 16.0, 11.0, 5.0 Hz), 4.0 (1H, m), 4.01 (1H, m), 4.85 (1H, d, J = 10.5 Hz), 7.01–8 (1H, d, J = 8.8 Hz), 7.1–7.25 (3H); MS, *m/z*: 285 (1) (M^+-H_2O), 260 (10) ($M^+-(CH_3)_2CH$), 216 (92) ($M^+-(CH_3)_2CH$-$CH(OH)CH_2$), 188 (21) (216−CO), 172 (11) ($216-CO_2$), 130 (100) ($C_{10}H_{10}$).

4.5.3. *N*-[(3*R*)-3-Hydroxy-5-phenyl-pentanoyl]-(4*S*,5*S*)-tetrahydronaphthalene-(1,2-*d*)-oxazolidin-2-one 12. Colourless syrup; $[\alpha]_D$ = +177.8 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.8–1.95 (2H), 2.06 (1H, dddd, J = 11.0, 11.0, 10.8, 4.3 Hz), 2.37 (1H, m), 2.7–2.85 (2H), 2.99 (1H, ddd, J = 15.2, 8.7, 4.3 Hz), 3.14 (1H, dd, J = 17.6, 9.4 Hz), 3.18 (1H, ddd, J = 15.2, 10.8, 5.4 Hz), 3.43 (1H, dd, J = 17.6, 2.7 Hz), 4.02 (1H, dd, J = 11.0, 10.5, 6.9 Hz), 4.23 (1H, m), 4.83 (1H, d, J = 10.5 Hz); ^{13}C NMR ($CDCl_3$): δ 22.30 (t), 25.90 (t), 29.88 (t), 32.00 (t), 38.30 (t), 44.11 (d), 61.60 (d), 67.28 (d), 123.64 (d), 126.11 (d), 126.77 (d), 127.87 (d), 128.65 (d), 2 × 128.66 (d), 2 × 128.67 (d), 134.12 (s), 135.26 (s), 141.87 (s), 155.42 (s), 175.94 (s); MS *m/z* (%): 347 (40) (M^+-H_2O), 130 (88) ($C_{10}H_{10}$), 91 (100) ($C_6H_5CH_2$).

4.6. Removal of the chiral auxiliary in β-hydroxyacyl-oxazolidinones 6, 8 and 10

4.6.1. Typical procedure. An aqueous solution (0.3 mL) of lithium hydroxide (5 mg, 0.2 mmol) was added at 0 °C to aldol adduct **10** (0.033 g, 0.1 mmol) in THF (1.5 mL). The resulting mixture was stirred at 0 °C, and the reaction monitored by TLC (silica gel, eluting with *n*-hexane/ethylacetate 1:1). After 1 h, the reaction mixture was quenched with sodium bicarbonate and extracted with ethylacetate (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure to give 0.015 g of crude oxazolidinone. The aqueous layer was acidified with HCl and then extracted with 3 mL portion of methylene chloride. The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure to give (*R*)-3-hydroxy-3-phenyl propionic acid[19] (13.2 mg, 79.5%): $[\alpha]_D$ = +21.5 (*c* 2, MeOH); ^1H NMR ($CDCl_3$ + D_2O): δ 2.78 and 2.82 (2H, ABX system, J_{AB} = 16.0; J_{AX} = 9.0; J_{BX} = 4.0 Hz), 5.18 (1H, dd, J = 9.0, 4.0 Hz), 7.2–7.5 (5H, aromatic protons). The same protocol applied to β-hydroxyacyloxazolidinone **6** gave (*R*)-3-hydroxy-4-methylpentanoic acid;[19] $[\alpha]_D$ = +39.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O): δ 0.94 (6H, d, J = 6.5 Hz), 1.72 (1H, m), 2.44 and 2.53 (2H, ABX system, J_{AB} = 16.2; J_{AX} = 3.0; J_{BX} = 9.7 Hz), 3.81 (1H, m). The protocol was applied to β-hydroxyacyloxazolidinone **8** and afforded (*R*)-3-hydroxy-4,4-dimethyl pentanoic acid[19]: $[\alpha]_D$ = +50.5 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O): δ 0.95 (9H, s), 2.45 and 2.62 (ABX system, J_{AB} = 16.0; J_{AX} = 9.5; J_{BX} = 3.0 Hz), 3.78 (1H, m).

4.7. Synthesis of *p*-toluenesulfonylamide 4

To a solution of amino alcohol **1** (0.3 g, 1.84 mmol) and 2,4-dimethylaminopyridine (0.03 g) in methylene chloride (10 mL), a solution of *p*-toluenesulfonyl chloride (0.35 g) in methylene chloride (3 mL) was added dropwise in about 30 min. The reaction was monitored by thin layer chromatography (SiO_2; ethylacetate/*n*-hexane 3:7) and stirred for 24 h at room temperature. Water (2 mL) was added and the aqueous phase extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was crystallized from dichloromethane–hexane and afforded pure **4** in 60% yields.

4.7.1. (1*S*,2*S*)-1-*p*-Tolylsulfonamido-2-hydroxy-1,2,3,4-tetrahydronaphthalene 4. Mp = 139–140 °C (ethylacetate/*n*-hexane); $[\alpha]_D$ = +33.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.90 (1H, m), 2.18 (1H, m), 2.48 (3H, s), 2.86 (2H, m), 3.96 (1H, m), 4.29 (1H, dd, J = 6.8, 6.7 Hz), 4.68 (1H, d, J = 6.8 Hz), 6.74 (1H, d, J = 6.5 Hz), 7.0–7.1 (3H), 7.40 (2H, d, J = 7.3 Hz), 7.90 (2H, d, J = 7.3 Hz); EI MS, *m/z* (%): 299 (1) (M^+-H_2O), 162 (98) ($M^+-CH_3C_6H_5SO_2$), 146 (59) ($M^+-CH_3C_6H_5SO_2NH_2$), 118 (100) ($M^+-CH_3C_6H_5SO_2NH_2-CO$). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.35; H, 5.99. Found: C, 64.75; H, 5.68.

4.8. Synthesis of 2-(bromoacyloxy)-*p*-toluenesulfonylamide 5

To a solution of **4** (0.188 g, 0.59 mmol) and dry triethylamine (0.14 mL) in methylene chloride (7 mL), a solution of α-bromoacetyl chloride (0.05 g) in dry methylene chloride (1 mL) was added dropwise in about 30 min. The reaction was monitored by thin layer

chromatography (SiO_2; ethylacetate/*n*-hexane 4:6) and stirred for 15 h at room temperature. Water (3 mL) was added and the aqueous phase extracted with dichloromethane (3×5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was chromatographed (SiO_2; ethylacetate/*n*-hexane 4:6) and afforded pure **5** in 80% yields.

4.8.1. (1*S*,2*S*)-1-*p*-Tolylsulfonamido-2-(α-bromoacetyl)-1,2,3,4-tetrahydronaphthalene 5. Mp = 132–133 °C (ethyl- acetate/*n*-hexane); $[\alpha]_D = +35.1$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.07 (2H, m), 2.49 (3H, s), 2.88 (2H, m), 3.50 (1H, d, $J = 14.3$ Hz), 3.81 (1H, d, $J = 14.3$ Hz), 4.6 (1H, dd, $J = 6.8$, 6.8 Hz), 4.7 (1H, d, $J = 6.8$ Hz), 5.17 (1H, m), 7.0–7.1 (4H), 7.4 (2H, d, $J = 7.7$ Hz), 7.82 (2H, d, $J = 7.7$ Hz); EI MS, *m*/*z* (%): 439–437 (1) (M^+), 299 (8) (M^+, $-BrCH_2COOH$), 144 (100) ($299-CH_3C_6H_5SO_2$), 128 (36) ($299-CH_3C_6H_5SO_2NH_2$). Anal. Calcd for $C_{19}H_{20}BrNO_4S$: C, 52.05; H, 4.57. Found: C, 52.25; H, 4.37.

4.9. Synthesis of β-hydroxyesters 13

A solution of **5** (0.172 g, 0.39 mmol) and isobutyraldehyde (0.58 mmol, 0.053 mL) in dry tetrahydrofurane (1 mL) was added dropwise in about 30 min at −78 °C, to a tetrahydrofuran solution of samarium iodide (0.1 M, 0.89 mmol). The reaction was monitored in thin layer chromatography (SiO_2; eluting with ethylacetate/*n*-hexane 3:7) and stirred at −78 °C for an additional 2.5 h. A diluted HCl solution (0.1 M, 9 mL) was then added and the aqueous phase extracted three times with ethylacetate (3×5 mL). The combined organic extracts were washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure to afford the crude material, which was purified by column chromatography (SiO_2; eluting with ethylacetate/*n*-hexane) and afforded the mixture of the two diastereoisomers in 50% yields. ^1H NMR ($CDCl_3$): δ 0.88 (3H, d, $J = 6.7$ Hz), 0.92 (3H, d, $J = 6.7$ Hz), 1.6 (1H, m), 2.0–2.3 (4H, m), 2.47 (3H, s), 2.86 (2H, m), 3.65 (0.5H, m, CHOH of one diastereoisomer), 3.7 (0.5H, m, CHOH of the other diastereoisomer), 4.58 (1H, dd, $J = 7.3$, 7.2 Hz), 4.8 (1H, d, $J = 7.3$ Hz), 5.2 (1H, m), 6.95–7.1 (4H), 7.36 (2H, d, $J = 7.33$ Hz), 7.85 (2H, d, $J = 7.33$ Hz); MS, *m*/*z*: 431 (M^+).

Acknowledgements

Universita' degli Studi di Milano and MIUR (Ministero dell' Istruzione, dell' Universita' e della Ricerca) are acknowledged for financial support (FIRB: Project code no. RBAU017KFW—COFIN 2002, Project code no. 2002058141-007).

References

1. Review: Ager, D. J.; Prakash, I.; Schaad, R. *Aldrichim. Acta* **1997**, *30*, 3–11; See also: Senanayake, C. H. *Aldrichim. Acta* **1998**, *31*, 1–15.
2. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1981**, *104*, 1737–1739.
3. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
4. Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.
5. Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339–1350.
6. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
7. (a) Park, C. H.; Britelli, D. R.; Wang, C. L. J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156–1165; (b) Grega, K. C.; Barbachyn, M. R.; Brickner, S. J.; Mizsak, S. A. *J. Org. Chem.* **1995**, *60*, 5255–5261.
8. Review: Ager, D. J.; Prakash, I.; Schaad, R. *Chem. Rev.* **1996**, *96*, 835–876.
9. (a) Ager, D. J.; Prakash, I.; Schaad, R. *Synthesis* **1996**, 1283–1285; (b) Prashad, M.; Kim, H. Y.; Har, D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1998**, *39*, 9369–9372.
10. Pettit, G. R.; Grealish, M. P. *J. Org. Chem.* **2001**, *66*, 8640–8642.
11. Orsini, F.; Pelizzoni, F.; Pulici, M.; Vallarino, L. M. *J. Org. Chem.* **1994**, *59*, 1–3.
12. Molander, G. A.; Harris, C. *Chem. Rev.* **1996**, *96*, 307–338; Fukuzawa, S.-i.; Matsuzawa, H.; Yoshimitsu, S.-i. *J. Org. Chem.* **2000**, *65*, 1702–1707.
13. (a) Ghosh, A. K.; Onischi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527–2528; (b) Ghosh, A. K.; Fidanze, S.; Onischi, M. J.; Hussai, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171–7174; (c) Ghosh, A. K.; Mathivanan, P. *Tetrahedron: Asymmetry* **1996**, *7*, 375–378; (d) Ghosh, A. K.; Chen, Y. *Tetrahedron* **1995**, *36*, 6811–6814.
14. Orsini, F.; Sello, G.; Bestetti, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2961–2969.
15. Sometimes with commercial samarium iodide, the colour changed during the addition of the organic reagents and an excess had to be added to complete the reaction.
16. In some runs, when the colour of the solution turned yellow before the end of the reaction and no more samarium was added, a significant amount of α-iodoacyloxazolidinone was isolated.
17. Fukuzawa, S.-i.; Matsuzawa, H.; Yoshimitsu, S.-i. *J. Org. Chem.* **2000**, *65*, 1702–1706.
18. Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766–770.
19. Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; Gonzales, A.; Garcia, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193–8200.