Tetrahedron 64 (2008) 10664–10669

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A concise and efficient route to the Alzheimer's therapeutic agent (*R*)-arundic acid

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ARTICLE INFO

Article history:
Received 29 July 2008
Received in revised form 5 September 2008
Accepted 5 September 2008
Available online 18 September 2008

Keywords:
Alzheimer
Camphor
Chiral auxiliary
Diastereoselective
Asymmetric alkylation

ABSTRACT

A short and efficient procedure for the preparation of (*R*)-arundic acid, a therapeutic agent for the treatment of Alzheimer's disease, has been developed. Based on cheap and commercially available (1*R*)-(+)-camphor as the source of chiral information, (*R*)-arundic acid is synthesized in a four-step cyclic sequence with 55% overall yield and high optical purity, ≥98% ee. Alkyl halide and acetylene constitute the only consumable carbon sources of this method, which allows obtaining of both enantiomers and recycling of chiral auxiliary.

1. Introduction

The Alzheimer's disease is a neurodegenerative process, which causes a progressive dysfunction of the central nervous system. It affects parts of the brain that control thought, memory and language thus inducing many undesired effects and severe behavioural changes. This disease, affecting specially to elderly population, is the most common form of dementia and it is becoming a major concern for human health.[1] Unfortunately, although a great effort is being devoted to the study of its origin, evolution, fight and prevention, only palliative treatments have been developed so far. Therefore, there is an increasing need to find new therapeutic agents, as is the case of (*R*)-arundic acid **1** ((*R*)-2-propyloctanoic acid). This promising compound, which is being tested in clinical studies, is considered a neuroprotective agent related to the inhibition of neuronal death.[2] It is active against Alzheimer's disease and also useful in therapy for stroke, amyotrophic lateral sclerosis and Parkinson's desease.[3]

But despite the importance of the development of an efficient method for the preparation of **1**, only few examples have been described. The first procedure, using the optical resolution of racemic 2-hexyl-4-pentynoic acid,[4] gave poor yields (27%) due to the need of five recrystallization cycles to get a final enantiomeric purity of 90% ee.[5] Next published methods were based on the asymmetric alkylation of chiral enolates. When L-prolinol was chosen as chiral auxiliary, arundic acid was prepared in 20% overall yield after a single recrystallization (96% ee).[6] Hasegawa et al.,[7] using Oppolzer's camphorsultam,[8] obtained the acid **1** with >99% ee after two recrystallizations (59% overall yield), but the expensive chiral auxiliary could not be recycled. The same group developed a new chiral auxiliary[9] derived from (*S*)-(−)-1-phenylethylamine, which allowed to obtain crystalline intermediates with moderate diastereoselectivity, 50–69% de, which could be increased to 99% de after two recrystallizations (10% overall yield). Piva et al.[10] prepared **1** with moderate optical purity, 88% ee, after eight steps (47% overall yield) via the diastereoselective photodeconjugation of a chiral diacetone-D-glucosyl α,β-unsaturated ester. From a different approach, Hasegawa's group[11] has also developed a more cost-effective process based on (*R*)-1,2-epoxyoctane, previously obtained by Jacobsen's[12] hydrolytic kinetic resolution of racemic epoxide. After five more steps and recrystallization of a crystalline intermediate, the product is prepared with 99.8% ee (52% overall yield). Enantiomerically pure (*R*)-arundic acid has been synthesized via metal mediated crotylation of (*R*)-2,3-cyclohexylideneglyceraldehyde,[13] after chromatographic isolation of the desired diastereomer from a three isomer mixture (eight steps, 13% overall yield).

Here, we wish to report a new and efficient synthesis of (*R*)-arundic acid **1**, which is obtained with high enantiomeric purity, ≥98% ee, and good overall yield, 55%, after four reaction steps.

2. Results and discussion

As shown before, the use of chiral auxiliary has been the most attempted way to prepare (*R*)-arundic acid. This well known and common methodology usually starts from the carboxylic acids to which the chiral auxiliary is covalently bonded through the acyl

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doi:10.1016/j.tet.2008.09.026

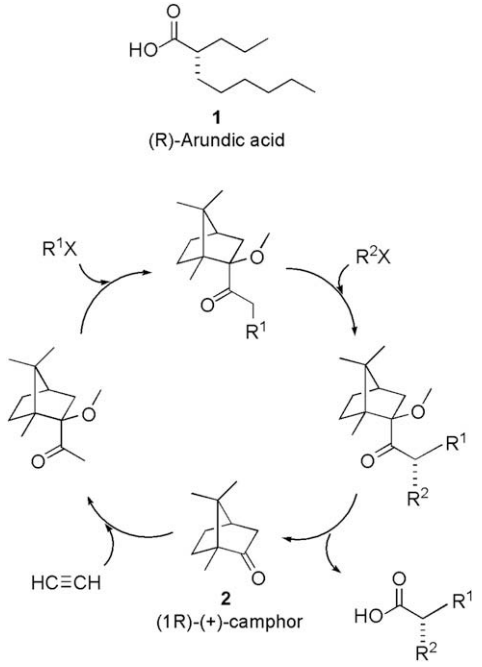
moiety.[14] Although there is no problem of chemo- and regioselectivity during enolate formation and subsequent alkylation, the insufficient reactivity of the enolates towards aliphatic halides is, with few exceptions,[15] one of the limitations associated with that approach. This makes necessary the use of more reactive alkyl halides, such as substituted allyl and propargyl halides, and, in consequence, an additional reduction step is required to get the target molecule. In addition, in case the desired diastereoselectivity is not reached in the selected synthetic method, the need to obtain crystalline intermediates that would allow optical enrichment by recrystallization constitutes another important difficulty for this specific compound, which has two aliphatic chains that make it highly lipophilic. Inherently, loss of product and lower yields are expected drawbacks of recrystallization steps. Those main inconveniences, encountered in the previously reported methods, are avoided in this new procedure.

This alternative synthesis is based on the cheap and commercially available auxiliary (1*R*)-(+)-camphor **2** as the source of chiral information, Scheme 1. In the design of this approach, acetylene is the elementary source of acetyl, and the corresponding alkyl halides, R^1X and R^2X, constitute the only consumable carbon sources of the method, which are in turn incorporated into the final product. During the alkylation process, (1*R*)-(+)-camphor **2**, directs the chemo-, regio- and diastereoselective incorporation of the two alkyl units in a stepwise fashion. At the end of the sequence, camphor is regenerated for reuse, with concomitant liberation of the target α-branched carboxylic acid.

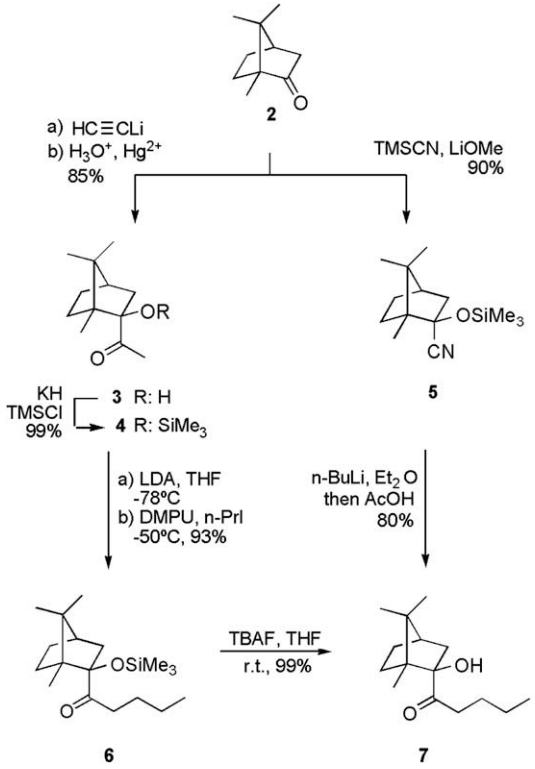
Since almost optically pure products are obtained in the key asymmetric alkylation step, which proceeds with essentially complete diastereoselectivity, there is no need of diastereomer separation or further optical purity enrichment by recrystallization. This is the most important feature of the procedure and determines the high efficiency of the synthesis. The successful alkylation reaction achieved with both reactive and less reactive primary aliphatic halides constitutes the third important contribution of this method. And last, both enantiomer of arundic acid can be prepared with similar enantiomeric purity and yield using the same methodology. This procedure is the implementation of our previous study[16] about the alkylation of (1*R*)-(+)-camphor-derived α-hydroxy ketones to give α-branched ketones with good yields and enantiomeric purity and constitutes a clear and practical example of its potential as an efficient approach to obtain optically active compounds.

The starting point of the complete synthetic sequence, which presents alternative pathways, is the commercially available (1*R*)-(+)-camphor **2**, as shown in Scheme 2. First, acetylene is incorporated into **2** to provide, after hydration of the resulting intermediate, the methyl ketone **3** in 85% yield (100 mmol scale). This methyl ketone, upon silylation using *N*-trimethylsilyl-2-oxazolidinone (TMSO)/TfOH[17] in THF, affords **4** almost quantitatively. During the present work, in an attempt to further stress the practical use of reagent **4** for large scale work, we have found that the silylation of **3** to **4** can also be carried out using the KH/TMSCl/THF system, which is cheaper and gives a reproducible yield of 99% after distillation of the product (reaction tested on a 100 mmol scale). Silylated intermediate **4**, after enolate generation with LDA and subsequent alkylation with *n*-propyl iodide in the presence of DMPU (20 mol %), furnished ketone **6** in 93% isolated yield. Initial experiments revealed that this ketone was completely resistant to further alkylation with both *n*-hexyl iodide and 1-bromo-2-hexene. Nevertheless, the less sterically demanding α-hydroxy ketone **7**, prepared in 99% yield by desilylation of **6**, was successfully alkylated, vide infra. An alternative shorter route to this ketone **7** was envisaged via the trimethylsilyl cyanohydrin **5**, which is easily obtained (TMSCN,[18] LiOMe, rt, 4 h) from starting (1*R*)-(+)-camphor **2** in 90% yield on a 100 mmol scale. Then, addition of *n*-BuLi to **5** smoothly proceeds at 0 °C to give, after treatment with acetic acid, the ketone **7** in 80% yield (80 mmol scale, 15.2 g of pure product).

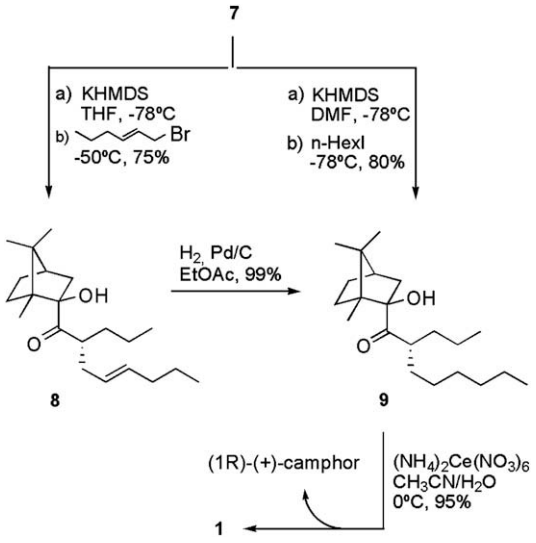
With ketone **7** in hand, completion of the synthesis of the anti-Alzheimer therapeutic agent **1** was accomplished as shown in Scheme 3. At this point, in the key asymmetric alkylation step, the use of potassium (potassium bis(trimethylsilyl)amide, KHMDS) as the counter ion in the enolate formation step was the major requirement for optimum results, since Li and Na enolates gave low conversions. Then, the alkylation of ketone **7** with reactive alkyl halides proceeded efficiently in THF as solvent, while for less reactive primary aliphatic halides, DMF was necessary to get the best



Scheme 1.



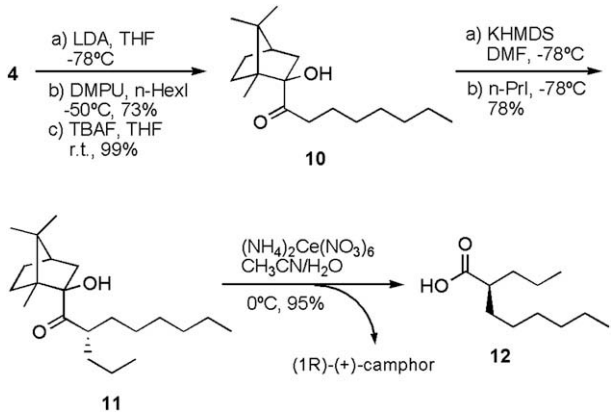
Scheme 2.



Scheme 3.

results. Thus, treatment of **7** with KHMDS in THF at −78 °C followed by exposure of the resulting enolate to 1-bromo-2-hexene at −50 °C furnished the alkylated product **8** in 75% isolated yield. But when the alkylation reaction was carried out with *n*-hexyl iodide, less than 20% of the alkylated product was formed. However, using DMF instead of THF, the reaction gave the desired product **9** in 80% yield. As expected from our previous studies,[16] in both cases only one diastereomer could be detected by ^{13}C NMR analysis of the corresponding crude reaction mixture, showing also that the same diastereoselectivity is achieved in the alkylation step using allylic halide or aliphatic halide. Hydrogenation of unsaturated ketone **8** produced **9** almost quantitatively. Finally, treatment of **9** with cerium ammonium nitrate (CAN) in acetonitrile–water afforded carboxylic acid **1** in 95% isolated yield with concomitant formation of the starting (1*R*)-(+)-camphor **2**, which was recovered pure in 90% yield. Therefore, in summary, following the short way, **2**→**5**→**7**→**9**→**1**, (*R*)-arundic acid is prepared in four steps and 55% overall yield.

In order to show the ability of this method to produce both enantiomers, the *S* enantiomer of **1** was also prepared following the sequence shown in Scheme 4. First, ketone **10** was prepared by selective monoalkylation of the methyl ketone **4** as previously described for similar compound **7**, followed by O-desilylation of the resulting intermediate (72% over the two steps). This was next alkylated with propyl iodide according to established conditions (**9** from **7**) to afford **11** in 78% isolated yield, which upon cleavage of the acyloin moiety afforded the carboxylic acid **12**. Overall yield of 45% after seven reaction steps from (1*R*)-(+)-camphor **2**.



Scheme 4.

Both enantiomers of arundic acid **1** and **12** were transformed into the corresponding amides by reaction with (*S*)-(−)-methylbenzylamine in order to confirm their final high optical purity by HPLC. The diastereomeric ratio for both amides was dr≥99:1 (see Supplementary data).

3. Conclusion

In conclusion, an alternative and efficient synthesis of anti-Alzheimer (*R*)-arundic acid **1** has been developed based on the essentially complete diastereoselective asymmetric alkylation of (1*R*)-(+)-camphor-derived α-hydroxy ketones. Almost enantiomerically pure product is obtained without diastereomer separation or recrystallization, thus allowing a good overall yield (55%). The consecutive alkylations can be achieved with both reactive and less reactive primary aliphatic halides and both enantiomers can be obtained by the same procedure. Big amounts of synthetic intermediates (80–100 mmol) are easily prepared by common procedures and the chiral auxiliary is recovered (90%) for reuse at the end of the sequence.

4. Experimental section

4.1. General

All reactions were carried out under an atmosphere of nitrogen in oven or flame-dried glassware with magnetic stirring and using dry solvents. Purification of reaction products was carried out by flash chromatography using silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60F PF_{254} plates. Melting points were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360-FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz, respectively, and are reported as δ values (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CHCl_3$ δ_C (77.00 ppm) as internal standards. Mass spectrometry (EIMS) was performed on a Finnigan GCQ (70 eV) using a 30 m J&W DB-5 ((5% phenyl)-methylpolysiloxane) column. Combustion analyses were performed on a Carlo Erba CHNS-O EA1108 elemental analyzer. Optical rotations were measured at 25±0.2 °C on a Jasco Polarimeter DIP-370 apparatus in methylene chloride or ethanol. Analytical high performance liquid chromatography (HPLC) was performed on a Waters chromatograph equipped with a diode array UV detector.

4.2. (1*R*)-2-*endo*-Acetyl-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol (3)

To a solution of lithium acetylide, ethylenediamine complex (11.96 g, 130 mmol) in THF (250 mL) at 0 °C was added (*R*)-(+)-camphor (15.22 g, 100 mmol) and the reaction mixture was warmed to 40 °C and stirred overnight.[19] The resulting solution was cooled in an ice-bath and quenched by the slow addition of water (160 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a mixture of ethynyl carbinols, *endo*/*exo* 97:3, as a dark oil. This crude material was dissolved in acetone (300 mL) and added dropwise over a period of 1.5 h to a warmed (60 °C) mixture prepared previously as follows: in a three-necked round-bottomed flask, equipped with a reflux condenser, a magnetic stirrer bar and a dropping funnel, red mercuric oxide (1.3 g, 6 mmol) was dissolved in a solution of concentrated sulfuric acid (2.1 mL), water (53 mL) and acetone

(75 mL). The resulting reaction mixture was stirred at 60 °C for an additional 15 min and allowed to cool. A saturated aqueous solution of $NaHCO_3$ (250 mL) was added to the reaction mixture, the solvent was removed under reduced pressure and CH_2Cl_2 (350 mL) was added. The aqueous layer was separated and the organic layer was washed with a saturated solution of $NaHCO_3$ (150 mL). The combined aqueous layers were extracted with CH_2Cl_2 and the organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the solid crude product was purified by crystallization from hexane. Yield of *endo*-2-acetylisoborneol: 16.7 g, 85%, mp 94–95 °C. $[\alpha]_D^{25}$ −65.6 (*c* 1.0, CH_2Cl_2); IR (neat) 3421, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 1H), 2.14–2.29 (m, 1H), 2.25 (s, 3H), 1.90–1.81 (m, 2H), 1.74–1.65 (m, 1H), 1.49–1.34 (m, 1H), 1.27–1.15 (m, 1H), 1.08 (s, 3H), 1.03–0.95 (m, 1H), 0.83 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 211.8, 87.4, 52.1, 50.3, 45.0, 40.9, 30.1, 27.6, 26.4, 20.8, 20.3, 10.5; EIMS *m*/*z* (%) 67 (23), 95 (100), 109 (38), 135 (45), 153 (83), 179 (52), 196 (4). Anal. Calcd for $C_{12}H_{20}O_2$ (196.32): C, 73.41; H, 10.29. Found: C, 73.06; H, 10.32.

4.3. (1*R*)-2-*endo*-Acetyl-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (4)

A solution of *endo*-2-acetylisoborneol obtained as above (19.6 g, 100 mmol) in dry THF (100 mL) was added dropwise to a mixture of KH (28 g, 250 mmol, 35% dispersion in mineral oil, previously washed with dry hexane) and THF (200 mL) at 0 °C. The resulting mixture was stirred at the same temperature for 10 min, then trimethylchlorosilane (19.2 mL, 150 mmol) was added, and the mixture stirred at room temperature for an additional 1 h. Water (100 mL) was then slowly added at 0 °C and, after completion of the addition, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined organic layer was washed with water (50 mL), dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure to give the crude product. This was purified by distillation to afford the title compound **4**. Yield: 26.6 g, 99%, mp 38 °C, bp 100 °C/0.05 mmHg. $[\alpha]_D^{25}$ −24.9 (*c* 1.0, CH_2Cl_2); IR (neat) 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51–2.45 (m, 1H), 2.15 (s, 3H), 1.77–1.69 (m, 2H), 1.57 (s, 1H), 1.11–1.05 and 1.40–1.26 (m, 1H), 0.80 (s, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 0.76–0.08 (m, 1H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 209.3, 90.7, 51.6, 50.9, 45.3, 39.7, 30.1, 26.9, 25.8, 21.0, 20.3, 11.4, 1.7; EIMS *m*/*z* (%) 73 (45), 93 (36), 107 (37), 117 (15), 169 (33), 225 (100), 268 (2). Anal. Calcd for $C_{15}H_{28}O_2Si$ (268.52): C, 67.09; H, 10.53. Found: C, 66.75; H, 10.56.

4.4. (1*R*)-2-*exo*-Trimethylsilyloxy-1,7,7-trimethylbicyclo-[2.2.1]heptane-2-carbonitrile[18] (5)

A solution of lithium methoxide (0.23 g, 6.0 mmol) and trimethylsilyl cyanide (16 mL, 120 mmol) in THF (200 mL) was stirred at room temperature for 10 min and then (*R*)-(+)-camphor (15.2 g, 100 mmol) was added and the mixture was stirred for 4 h. Then CH_2Cl_2 (100 mL) was added and the mixture was washed with a saturated aqueous solution of Na_2CO_3 (2×50 mL). The organic extract was dried over $MgSO_4$, filtered and the solvent was evaporated to afford the *endo*/*exo* mixture (96:4). Purification by flash column chromatography (1:30 EtOAc/hexane) gave the *endo* isomer: 22.6 g, 90%, bp 147 °C/9 mmHg. $[\alpha]_D^{25}$ −31.0 (*c* 1.2, CH_2Cl_2); IR (neat) 2230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23–2.12 (m, 1H), 2.05–1.99 (m, 1H), 1.89–1.49 (m, 4H), 1.23–1.01 (m, 1H), 0.96, 0.92 and 0.85 (s, 3H), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 121.9, 78.5, 54.1, 48.6, 47.8, 45.1, 31.7, 26.5, 21.1, 20.5, 10.6, 1.1; EIMS *m*/*z* (%) 67 (19), 95 (100), 237 (1). Anal. Calcd for $C_{14}H_{25}NOSi$ (251.46): C, 66.87; H, 10.02; N, 5.57. Found: C, 66.92; H, 10.06; N, 5.60.

4.5. (1*R*)-2-*endo*-Pentanoyl-2-*exo*-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane (6)

A solution of diisopropylamine (4.1 mL, 29.1 mmol) in THF (60 mL) was cooled to −78 °C and *n*-butyllithium (2.5 M in hexane, 11.6 mL, 29.1 mmol) was added dropwise. After 30 min, a solution of **4** (6.0 g, 22.4 mmol) in THF (50 mL) was added dropwise and stirring was continued at −78 °C for 2 h. Then DMPU (22.4 mL) and propyl iodide (15.2 mL, 134.2 mmol) were successively added at the same temperature and the mixture was stirred at −50 °C for 4 h. The reaction was quenched at −50 °C with 120 mL of 1 N HCl, and the mixture was allowed to reach room temperature. The aqueous phase was extracted with hexane (3×100 mL) and the combined organic layers were washed with water (5×80 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give **6**. Yield: 6.46 g, 93%. IR (neat) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 (ddd, 1H, *J*=5.6, 9.7, 17.6 Hz), 2.53 (d, 1H, *J*=11.7 Hz), 2.33 (ddd, 1H, *J*=5.6, 9.7, 17.6 Hz), 1.79–1.68 (m, 2H), 1.66–1.42 (m, 3H), 1.40–1.25 (m, 3H), 1.18–1.08 (m, 1H), 1.04 (s, 3H), 0.99 (s, 3H), 0.92 (t, 3H, *J*=7.0 Hz), 0.81 (s, 3H), 0.79–0.67 (m, 1H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 211.8, 90.7, 51.6, 50.8, 45.2, 40.2, 38.1, 29.9, 29.7, 26.1, 25.7, 22.7, 20.9, 20.3, 14.0, 11.3, 1.6; EIMS *m*/*z* (%) 73 (38), 93 (33), 107 (28), 135 (31), 225 (100). Anal. Calcd for $C_{18}H_{34}O_2Si$ (310.55): C, 69.62; H, 11.04. Found: C, 69.69; H, 11.09.

4.6. (1*R*)-2-*endo*-Pentanoyl-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol (7)

From ***5***. To a solution of **5** (20.1 g, 80 mmol) in Et_2O (240 mL) at 0 °C was added a solution of BuLi in hexane (2.5 M, 64 mL, 160 mmol) and the mixture was stirred at the same temperature for 2 h. Then, acetic acid (30 mL) was added and stirred for 1 h at 0 °C. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added and the mixture was extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (1:30 EtOAc/hexane) gave *endo*-2-pentanoylisoborneol. Yield: 15.2 g, 80%.

From ***6***. Ketone **6** (6.21 g, 20 mmol) was dissolved in THF (200 mL) and TBAF (1.0 M in THF, 30.5 mL, 30.5 mmol) was added. The resulting mixture was stirred at room temperature for 1 h, then filtered trough a pad of silica gel, and the filtrate evaporated under reduced pressure. The residue was purified by flash column chromatography (1:20 EtOAc/hexane) to give **7**. Yield: 4.7 g, 99%. $[\alpha]_D^{25}$ −55.7 (*c* 1.1, CH_2Cl_2); IR (neat) 3489, 2944, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s, 1H), 2.71 (ddd, 1H, *J*=6.3, 8.1, 17.0 Hz), 2.44 (ddd, 1H, *J*=6.3, 8.1, 17.0 Hz), 2.24 (d, 1H, *J*=12.6 Hz), 1.89–1.79 (m, 2H), 1.75–1.41 (m, 3H), 1.40–1.17 (m, 4H), 1.09 (s, 3H), 0.91 (s, 3H), 0.90 (t, 3H, *J*=7.1 Hz), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.6, 87.2, 52.5, 50.2, 45.0, 40.8, 39.3, 30.0, 26.6, 26.3, 22.4, 20.7, 20.3, 13.9, 10.4. Anal. Calcd for $C_{15}H_{26}O_2$ (238.37): C, 75.58; H, 10.99. Found: C, 75.68; H, 11.03.

4.7. (1*R*)-2-*endo*-[(2*R*)-Propyloct-4-enoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (8)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 46 mL, 23 mmol) was added dropwise to a solution of the starting ketone **7** (2.4 g, 10 mmol) in dry THF (40 mL) at −78 °C under nitrogen atmosphere and the mixture was stirred for 4 h at the same temperature. 2-Hexenyl bromide (3.3 g, 20 mmol) was added and the reaction was allowed to reach −50 °C and was stirred at this temperature until completion (1 h). The reaction was quenched at −50 °C with 50 mL of saturated aqueous NH_4Cl and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2

(2×50 mL). The combined organics were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the product was effected by flash column chromatography (1:30 EtOAc/hexane). Yield: 2.4 g, 75%. $[\alpha]_D^{25}$ −62.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3529, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.39 (m, 1H), 5.32 (m, 1H), 2.93 (m, 1H), 2.75 (s, 1H), 2.30–0.81 (m, 16H), 2.19 (d, 1H), 1.09–0.81 (3s, 9H), 1.09–0.82 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 217.3, 133.1, 127.0, 87.3, 53.0, 50.3, 47.1, 45.0, 41.3, 35.0, 34.6, 33.7, 29.6, 26.9, 22.5, 20.8, 20.7, 20.3, 14.3, 13.6, 10.4; EIMS *m*/*z* (%) 67 (14), 95 (42), 109 (67), 135 (48), 153 (100), 321 (1). Anal. Calcd for $C_{21}H_{36}O_2$ (320.57): C, 78.68; H, 11.34. Found: C, 78.91; H, 11.39.

4.8. (1*R*)-2-*endo*-[(2*R*)-Propyloctanoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (9)

From **7**. A solution of **7** (2.4 g, 10 mmol) in DMF (30 mL) was added dropwise over a solution of potassium bis (trimethylsilyl)amide (0.5 M in toluene, 50 mL, 25 mmol) in DMF (30 mL) at −78 °C and the mixture was stirred for 4 h at the same temperature. Hexyl iodide (4.4 mL, 30 mmol) was added and the mixture stirred for 2 h. The reaction was quenched with 50 mL of saturated aqueous NH_4Cl and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (2×50 mL). The combined organic extracts were washed with water (80 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification was effected by silica gel flash column chromatography (1:30 EtOAc/hexane). Yield: 2.6 g, 80%.

From ***8***. To a solution of **8** (3.2 g, 10 mmol) in ethyl acetate (40 mL), 10% palladium on charcoal (1 g, 1 mmol) was added and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature for 1 h and then the suspension was filtered through a pad of Celite, washed with ethyl acetate (2×50 mL) and the solvent was evaporated to yield the product, which was purified by column chromatography (1:15 EtOAc/hexane). Yield: 3.20 g, 99%, bp 130 °C/0.34 mmHg. $[\alpha]_D^{25}$ −69.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3508, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (m, 1H), 2.44 (s, 1H), 2.18–2.11 (d, 1H), 2.18–0.83 (m, 20H), 1.09–0.81 (3s, 9H), 0.96–0.81 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 218.0, 86.9, 53.1, 50.2, 47.0, 45.0, 41.1, 33.5, 32.0, 31.7, 29.6, 29.6, 27.3, 27.0, 22.6, 21.0, 20.9, 20.3, 14.5, 14.1, 10.4; EIMS *m*/*z* (%) 67 (9), 95 (45), 109 (42), 135 (41), 153 (100), 322 (3). Anal. Calcd for $C_{21}H_{38}O_2$ (322.53): C, 78.20; H, 11.88. Found: C, 78.44; H, 11.95.

4.9. (*R*)-2-Propyloctanoic acid (1)

To a solution of α′-hydroxy ketone **9** (3.2 g, 10 mmol) in acetonitrile (120 mL) at 0 °C was added dropwise a solution of cerium ammonium nitrate (CAN) (16.4 g, 30 mmol) in water (60 mL) and the mixture was stirred at the same temperature for 1 h. Then water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with 2 N NaOH (3×70 mL), dried over $MgSO_4$, filtered and the solvent evaporated to afford the starting (*R*)-(+)-camphor in 85–90% yield.[20] The basic aqueous layer was acidified by adding concentrate HCl and then extracted with EtOAc (3×100 mL). The combined extracts were dried over $MgSO_4$, filtered, the solvent removed under reduced pressure and the crude product purified by column chromatography (1:30 EtOAc/hexane) to afford pure **1**. Yield: 1.8 g, 95%, bp 120–121 °C/1 mmHg. $[\alpha]_D^{25}$ +6.5 (*c* 1.0, EtOH); IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.54 (s, 1H), 2.34–2.23 (m, 1H), 1.65–1.20 (m, 14H), 0.88–0.81 (t, 3H, *J*=7.0 Hz), 0.84–0.81 (t, 3H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 183.3, 45.4, 34.4, 32.2, 31.7, 29.3, 27.4, 22.7, 20.6, 14.1, 14.0. Anal. Calcd for $C_{11}H_{22}O_2$ (186.30): C, 70.92; H, 11.90. Found: C, 70.99; H, 11.95.

4.10. (1*R*)-2-*endo*-Octanoyl-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol (10)

Following the same procedure previously described for compound **6**, from methyl ketone **4** (5.37 g, 20 mmol) and hexyl iodide (17.7 mL, 120 mmol), 5.15 g, 73%, of the silylated ketone were obtained. ^1H NMR ($CDCl_3$) δ 2.71 (ddd, 1H, *J*=5.6, 9.6, 17.6 Hz), 2.52 (d, 1H, *J*=11.7 Hz), 2.31 (ddd, 1H, *J*=5.7, 9.5, 17.6 Hz), 1.79–1.46 (m, 5H), 1.38–1.20 (m, 9H), 1.19–1.10 (m, 1H), 1.03 (s, 3H), 0.98 (s, 3H), 0.89–0.70 (m, 4H), 0.80 (s, 3H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 211.8, 90.7, 51.6, 50.8, 45.2, 40.2, 38.5, 31.7, 29.9, 29.6, 29.2, 25.8, 24.0, 22.6, 20.9, 20.3, 14.1, 11.3, 1.7; EIMS *m*/*z* (%) 73 (72), 93 (66), 107 (63), 117 (28), 135 (53), 169 (38), 225 (100), 263 (5).

This trimethylsilyloxy ketone (5.0 g, 14.3 mmol) was then desilylated as shown for product **7** to obtain, after purification, 4.0 g, 99%, of the corresponding hydroxy ketone **10**. $[\alpha]_D^{25}$ −45.1 (*c* 1.0, CH_2Cl_2); IR (neat) 3519, 2920, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80 (s, 1H), 2.71 (ddd, 1H, *J*=7.0, 8.2, 17.2 Hz), 2.44 (ddd, 1H, *J*=6.2, 8.1, 17.1 Hz), 2.25 (d, 1H, *J*=12.5 Hz), 1.91–1.75 (m, 2H), 1.74–1.51 (m, 2H), 1.49–1.35 (m, 1H), 1.33–1.17 (m, 9H), 1.09 (s, 3H), 0.98–0.83 (m, 2H), 0.92 (s, 3H), 0.85 (d, 3H, *J*=6.9 Hz), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 214.6, 87.2, 53.7, 52.5, 50.2, 45.0, 40.8, 39.6, 31.7, 30.1, 29.2, 29.1, 26.6, 24.2, 22.6, 20.7, 20.3, 14.0, 10.4. Anal. Calcd for $C_{18}H_{32}O_2$ (280.44): C, 77.09; H, 11.53. Found: C, 77.24; H, 11.49.

4.11. (1*R*)-2-*endo*-[(2*S*)-Propyloctanoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (11)

Following the same procedure previously described to prepare **9** via **7**, from hydroxy ketone **10** (2.8 g, 10 mmol) and propyl iodide (3.4 mL, 30 mmol), 2.53 g, 78%, of pure dialkylated ketone **11** were obtained. $[\alpha]_D^{25}$ −58.0 (*c* 1.0, CH_2Cl_2); IR (neat) 3534, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (m, 1H), 2.85 (s, 1H), 2.15 (d, 1H), 1.96–0.57 (m, 20H), 1.09–0.81 (3s, 9H), 0.99–0.81 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 218.0, 87.0, 53.1, 50.2, 47.0, 45.0, 41.1, 34.2, 31.7, 31.4, 29.7, 29.7, 27.8, 27.0, 22.7, 20.9, 20.5, 20.3, 14.4, 14.1, 10.4. EIMS *m*/*z* (%) 67 (10), 95 (55), 109 (50), 135 (45), 153 (100), 322 (5). Anal. Calcd for $C_{21}H_{38}O_2$ (322.53): C, 78.20; H, 11.88. Found: C, 78.38; H, 11.95.

4.12. (*S*)-2-Propyloctanoic acid (12) ((*S*)-arundic acid)

Following the same procedure previously described for its enantiomer **1**, from α′-hydroxy ketone **11** (3.2 g, 10 mmol), 1.8 g, 95%, of carboxylic acid **12** were obatined. Bp 120–121 °C/1 mmHg. $[\alpha]_D^{25}$ −6.5 (*c* 1.0, EtOH); IR (neat) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.54 (s, 1H), 2.34–2.23 (m, 1H), 1.65–1.20 (m, 14H), 0.88–0.81 (t, 3H, *J*=7.0 Hz), 0.84–0.81 (t, 3H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 183.3, 45.4, 34.4, 32.2, 31.7, 29.3, 27.4, 22.7, 20.6, 14.1, 14.0. Anal. Calcd for $C_{11}H_{22}O_2$ (186.30): C, 70.92; H, 11.90. Found: C, 71.12; H, 11.86.

4.13. Preparation of amides from 1 or 12 for HPLC analysis

To a solution of the carboxylic acid **1** or **12** (46.6 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) cooled to 0 °C, was added dropwise oxalyl chloride (44 μL, 0.5 mmol). The reaction was stirred at the same temperature for 1 h. Then the solvent and the excess of oxalyl chloride were removed by evaporation under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL) and (*S*)-(−)-α-methylbenzylamine (43 μL, 0.30 mmol) and Et_3N (53 μL, 0.38 mmol) were added, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with water (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with 1 N HCl (2×15 mL), a saturated solution of $NaHCO_3$ (15 mL), and finally dried over $MgSO_4$ and concentrated. The crude products were analyzed by HPLC to

determine the diastereoisomeric excesses (RP-18 column, CH_3CN/H_2O 47:53, 0.5 mL/min).

Acknowledgements

This work was financially supported by Fundación Caja Navarra (CAN) (project no. 12758) and by Gobierno de Navarra. A grant to A.L. from UPNA is gratefully acknowledged.

Supplementary data

^1H and ^{13}C NMR spectra of compounds **1** and **3**–**11**. HPLC chromatograms of amides derived from **1** and **12**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.026.

References and notes

1. (a) Liuzzi, F. J.; Lasek, R. J. *Science* **1987**, *237*, 642–645; (b) Uchida, Y.; Tomonaga, M. *Brain Res.* **1989**, *481*, 190–193; (c) Moundijian, A.; Antel, J. P.; Yong, V. W. *Brain Res.* **1991**, *547*, 223–228.
2. Sorbera, L. A.; Castañer, J.; Castañer, R. M. *Drugs Future* **2004**, *29*, 441–448.
3. (a) Tateishi, N.; Ohno, H.; Kishimoto, K.; Ohuchida, S. Japan Patent 7-316092, 1995; *Chem. Abstr.* **1995**, *122*, 160096b; (b) Tateishi, N.; Mori, T.; Kagamiishi, Y.; Satoh, S.; Katsube, N.; Morikawa, E.; Morimoto, T.; Matsui, T.; Asano, T. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 723–734; (c) Matsui, T.; Mori, T.; Tateishi, N.; Kagamiishi, Y.; Satoh, S.; Katsube, N.; Morikawa, E.; Morimoto, T.; Ikuta, F.; Asano, T. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 711–722.
4. Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323–5326.
5. Kishimoto, K.; Nakai, H. Japan Patent 7-98328, 1995; *Chem. Abstr.* **1997**, *126*, 74487.
6. (a) Kishimoto, K.; Nakai, H. Japan Patent 7-102693, 1995; *Chem. Abstr.* **1997**, *126*, 74488; (b) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236; (c) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137–3139.
7. (a) Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423–428; (b) Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Iguchi, Y.; Yonekawa, Y.; Okamoto, M.; Ohta, C.; Hashimoto, S.; Ohuchida, S. *Org. Process Res. Dev.* **2003**, *7*, 168–171.
8. (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603–5606; (b) Oppolzer, W.; Rosset, S.; Brabander, J. De. *Tetrahedron Lett.* **1997**, *38*, 1539–1540.
9. Hasegawa, T.; Yamamoto, H. *Synthesis* **2003**, *8*, 1181–1186.
10. Peotier, B.; Holmes, T.; Piva, O. *Tetrahedron: Asymmetry* **2005**, *16*, 1513–1520.
11. Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Ohta, C.; Nakabayashi, K.; Okamoto, M.; Hamano, M.; Takahashi, K.; Ohuchida, S.; Hamada, Y. *Org. Process Res. Dev.* **2005**, *9*, 774–781.
12. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.
13. Goswam, D.; Chattopadhyay, A. *Lett. Org. Chem.* **2006**, *12*, 922–925.
14. For reviews, see: (a) Rück, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 433–435; (b) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451–2465; (c) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1151–1166; (d) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 357–373; (e) Fey, P. In *Stereoselective Synthesis (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, New York, NY, 1996; E21 Vol. 2.
15. (a) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zhaler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313; (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511; (c) Backes, B. J.; Dragoli, D. R.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 5472–5478; (d) Tessier, A.; Pytkowicz, J.; Brigaud, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3677–3681.
16. Palomo, C.; Oiarbide, M.; Mielgo, A.; González, A.; García, J. M.; Landa, C.; Lecumberri, A.; Linden, A. *Org. Lett.* **2001**, *3*, 3249–3252.
17. (a) Palomo, C.; González, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 180–182; (b) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193–8200.
18. Adapted from Wilkinson, H. S.; Grover, P. T.; Vandenbossche, P.; Bakale, R. P.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2001**, *3*, 553–556.
19. Adapted from Hung, S.-C.; Wen, Y.-F.; Chang, J.-W.; Liao, C.-C.; Uang, B.-J. *J. Org. Chem.* **2002**, *67*, 1308–1313.
20. (1*R*)-(+)-Camphor 100% ee: $[\alpha]_D^{25}$ +42.2 (*c* 1.0, EtOH). Recovered material: $[\alpha]_D^{25}$ +41.8 (*c* 1.0, EtOH).