Tetrahedron: *Asymmetry* 22 (2011) 603–608

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Synthesis of new enantiopure *trans*-3,4-diaminocaranes from (+)-3-carene

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ARTICLE INFO

Article history:
Received 14 February 2011
Accepted 28 February 2011
Available online 12 April 2011

ABSTRACT

A synthetic strategy to obtain new enantiopure *trans*-3,4-diaminocaranes derived from (+)-3-carene via a stereoselective methodology is described. The stereoselective preparation of 3,4-α-carene- or 3,4-β-carene-epoxide is followed by a ring opening by sodium azide to obtain the azido-alcohols. Subsequent cyclization affords the corresponding aziridine diastereoisomers, which are converted to azido amines by opening of the aziridine rings by sodium azide and then reduced to the final diamine diastereoisomers. The absolute configurations of the final diamines and of novel intermediates are established by ^{1}H NMR spectra correlated with conformational analysis supported by molecular modeling.

1. Introduction

Chiral vicinal diamines are very important molecules which have found application in several fields.[1–4] For instance, several synthetic diamine derivatives have been employed as medicinal agents, in particular in chemotherapy as substitutes for cisplatin.[5] Chiral 1,2-diamines are also used in catalytic asymmetric synthesis,[6] as chiral auxiliaries[4] and in organocatalysis.[7–11] They have also found use as chelating agents to obtain coordination compounds useful in homogeneous catalysis.[12–15]

Herein we report the synthesis of new enantiopure *trans*-3,4-diaminocaranes, derived from (+)-3-carene, an enantiomerically pure terpene, easily obtained from the 'chiral pool'. Terpenes are widely used in organic synthesis to obtain enantiomerically pure compounds,[16–21] chiral auxiliaries or asymmetric ligands employed in enantioselective transformations.[22–28] Moreover, chiral 1,2-diamines derived from (+)-3-carene are structurally correlated with *trans*-1,2-diaminocyclohexane analogues, widely used as chiral reagents, scaffolds and ligands for catalysis.[3,9]

The stereoselective epoxidation of (+)-3-carene **1** affords α-carene oxide **2**. The reaction of carene **1** with NaI in the presence of sulfuric acid and hydrogen peroxide affords β-carene oxide **10**. Epoxides **2** and **10** can be converted to the corresponding azido-alcohols **3** and **4** or **11** and **12**. Subsequent cyclization of azido alcohol **4** affords aziridine **5** but does not take place with azido alcohol **3**, and it is diastereoconvergent from azido-alcohols **11** and **12**, that both lead to aziridine **13**. The opening of the aziridine rings by sodium azide afforded to the corresponding azido-amines **6** and **7** or **14** and **15**, which can then be reduced to the final diamines diastereoisomers **8** and **16**.

2. Results and discussion

2.1. Synthesis of *trans*-(*R*,*R*)-3,4-diamino carane 8 from 3,4-α-carene oxide 2

The synthetic route to obtain *trans*-3,4-diamino carane **8** is described in detail in Scheme 1. The starting material (+)-3-carene **1** is converted to α-carene oxide **2** with MCPBA, according to the procedure reported by Brown and Suzuki.[29]

The second step is the formation of azido-alcohols **3** and **4** from α-carene oxide **2**. These products are obtained by heating α-carene oxide **2** in methanol at reflux with sodium azide and ammonium chloride.[30] The nucleophilic attack of NaN_3 on carene epoxide **2** is not diastereoselective, unlike that observed in the synthesis of analogous amines starting from limonene oxide:[28] the azido ion attacks both carbon atoms of epoxide ring of α-carene oxide **2**, forming two possible regioisomer azido-alcohols regioisomer **3** and **4** in similar amounts.

At this point, our aim was to prepare aziridine **5** from azido-alcohols **3** and **4** via a pseudo-Staudinger reaction,[31,32] this could be performed by treating the azido-alcohols with triphenylphosphine in 1,4-dioxane. However, the reaction of azido alcohol **3** with triphenylphosphine affords only a mixture of unidentified decomposition products, already at room temperature, while the regioisomer **4** forms the aziridine **5** directly at reflux. Therefore, it was necessary to find a method aimed to obtain exclusively azido alcohol **4** from α-carene oxide **2**, trying to get the highest possible yield of aziridine **5**. Treating *trans*-carene epoxide **2** with sodium azide in acetic acid and water enables a regioselective pH-controlled ring opening reaction to take place, forming the only regioisomer **4**,[33,34] as shown in Scheme 2. The regioselectivity of this reaction can be explained by considering that the attack of the azide ion takes place after protonation of the epoxide, which develops a more positive charge on the tertiary α-carbon with respect to the

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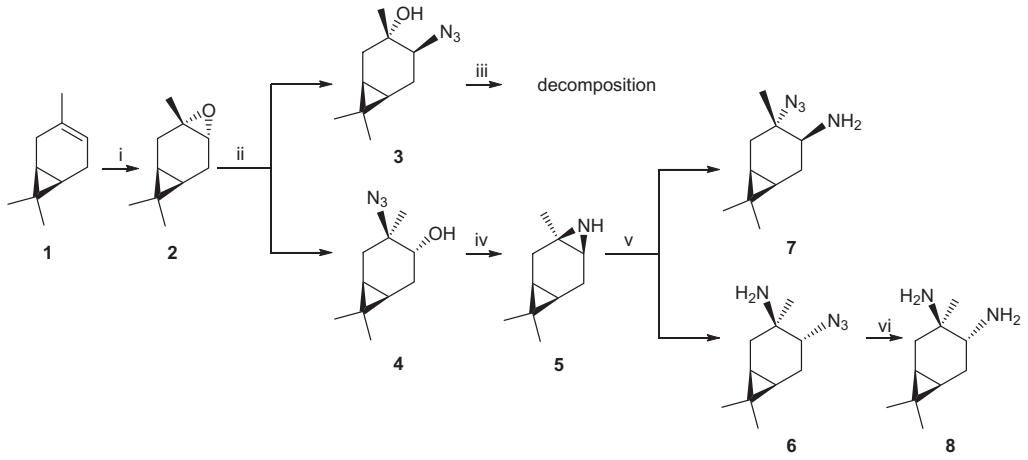
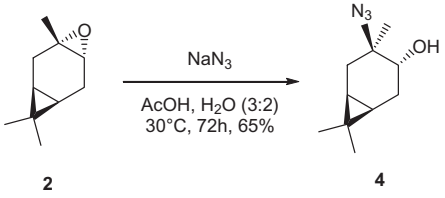
doi:10.1016/j.tetasy.2011.02.027



Scheme 1. Reagents and conditions: (i) MCPBA, $CHCl_3$, 0 °C, 70 min, 80%; (ii) NaN_3, NH_4Cl, MeOH, reflux, 32 h, 49%, **3**:**4** = 1:1.2; (iii) PPh_3, 1,4-dioxane, rt, 24 h; (iv) PPh_3, 1,4-dioxane, reflux, 24 h, 96%; (v) NaN_3, $CeCl_3{\cdot}7H_2O$, CH_3CN/H_2O, (5:1), reflux, 3 h, 37%, **6**:**7** = 36:1; (vi) $LiAlH_4$, MTBE, 0 °C to rt, 4 h, 97%.



Scheme 2.

secondary one. In this way only the more substituted α-carbon is activated to attack of the nucleophile azide ion.

The nucleophilic ring opening of aziridine **5** with sodium azide and $CeCl_3{\cdot}7H_2O$ as a catalyst shows very high selectivity towards azido amine **6** (Y = 36%) with respect to **1** which is formed in very poor yields (Y = 1%).

The last step is the reduction with $LiAlH_4$ of the azido group in azido amine **6** to an amine, to form *trans*-(*R*,*R*)-3,4-diamino carane **8**. This product is stable in air and does not need to be stabilized by salt formation with acids.

2.2. Synthesis of *trans*-(*R*,*R*)- and *trans*-(*S*,*S*)-3,4-diamino carane from β-carene oxide

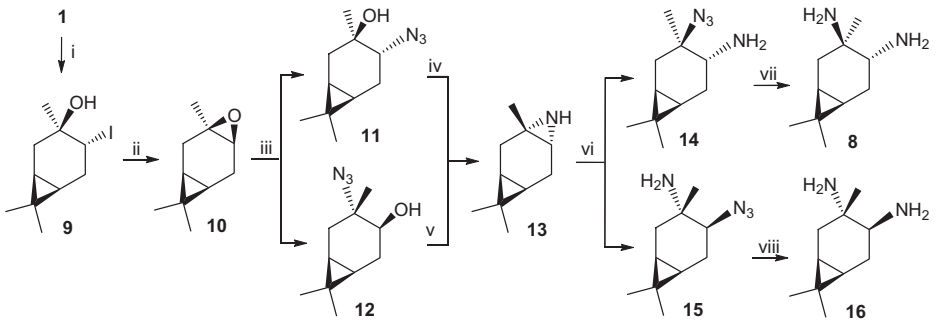
The synthetic route to obtain selectively *trans*-(*R*,*R*)- and *trans*-(*S*,*S*)-3,4-diamino caranes **8** and **16** is depicted in detail in Scheme 3.

When treating (+)-3-carene **1** with MCPBA only α-carene oxide **2** is obtained[35] (see Scheme 1). To get β-carene oxide **10** (+)-3-carene **1** is converted first into the haloidrine **9**,[36] then treated with NaH. The synthesis of *trans*-(*R*,*R*)- and *trans*-(*S*,*S*)-3,4-diamino caranes **8** and **16** proceeds from β-carene oxide **10** through the same synthetic sequence that produces diamine **8** from α-carene oxide **2**, as described in Scheme 3.

The azido-alcohols **11** and **12** are obtained by treating β-carene oxide **10** with NaN_3 and NH_4Cl.[30] The azido group is then converted into an aziridine again through a pseudo-Staudinger mechanism by reaction with triphenylphosphine[31,32] and also in this case a different reactivity of the two azido-alcohols is observed: azido alcohol **11** forms aziridine **13** at room temperature, while **12** needs heating in 1,4-dioxane at reflux to react. However, at this point the synthesis is diastereoconvergent, because both azidoalcohols afford to the same aziridine **13**. The aziridine **13** reacts with sodium azide in the presence of $CeCl_3{\cdot}7H_2O$ to give azido amines **14** and **15**. The reduction of azido amine **14** affords diamine **8** as previously obtained in the process starting from α-carene oxide **2**. Reduction of azido amine **15** using the same conditions affords the diamine **16**.

3. Stereochemistry

The absolute configuration of aziridine **5** in Scheme 1 was attributed on the basis of the fact that either azido alcohol **3** or azido alcohol **4**, whose configuration is confirmed by literature data,[30] afford the same product through a pseudo-Staudinger reaction, that takes place with retention of configuration of the carbon atom bearing the azido group, as was also observed in the case of limonene derivatives.[28,37,32]



Scheme 3. Reagents and conditions: (i) NaI, H_2SO_4, H_2O_2, H_2O/THF (1:2.3), 0 °C to rt, 12 h, 82%; (ii) NaH, THF/Et_2O (1:1), rt, 5.5 h, 84%; (iii) NaN_3, NH_4Cl, MeOH, reflux, 32 h, 72%, **11**:**12** = 1:1; (iv) PPh_3, 1,4-dioxane, rt, 24 h, 79%; (v) PPh_3, 1,4-dioxane, reflux, 36 h, 64%; (vi) NaN_3, $CeCl_3{\cdot}7H_2O$, CH_3CN/H_2O (5:1), reflux, 45 min, 92%, **14**:**15** = 1:2.2; (vii) $LiAlH_4$, MTBE, 0 °C to rt, 20 min, 85%; (viii) $LiAlH_4$, MTBE, 0 °C to rt, 70 min, 91%.

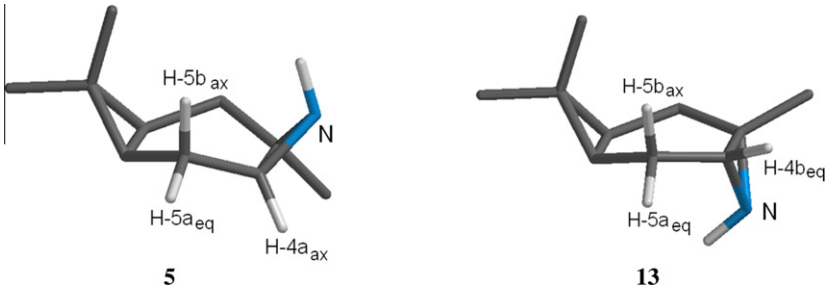


Figure 1. Simplified representation of the more stable conformation of diastereomer aziridines **5** and **13** (minimized at the semiempirical PM3 level[38]).

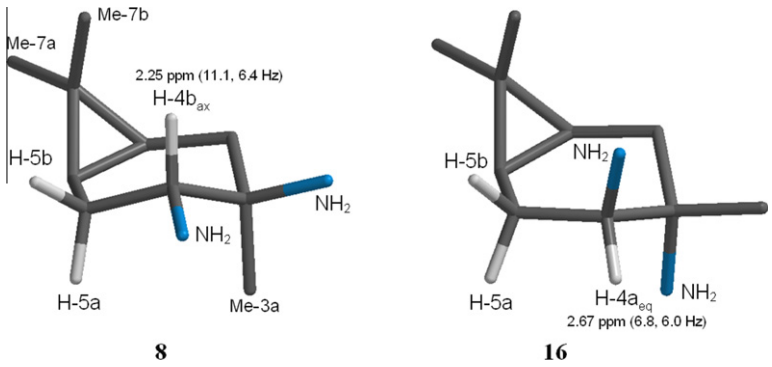


Figure 2. Exemplified representation of the more stable conformation of diastereomer trans-(3,4)-diaminocaranes **8** and **16** (minimized at the semiempirical PM3 level[14]).

These considerations are confirmed by some observations on the ^{1}H NMR spectra of aziridine **5** compared with the one of its diastereomer, aziridine **13**.

Aziridines **5** and **13**, depicted in Figure 1 in their most stable conformations, show values of the coupling constants $^3J_{4\text{-}5}$ of 7.6, 4.8 and 2.6, 2.6 Hz, respectively, in agreement with the values expected according to the Karplus rule for torsional angles $\phi = 15°$ and 130° in **5** and $\phi = 50°$ and 65° in **13**.

In the same way the attribution of the configurations of all the other compounds described was made in agreement with the interpretation of the ^{1}H-NMR data. Compounds **4**, **6**, **8**, **11**, and **14** show respectively $^3J_{4\text{-}5}$ values of 10.3, 10.7, 11.1, 11.1 and 11.1 Hz, typical of *trans*-diaxial hydrogen atoms (as shown for H-4b/H-5a in compound **8**, Fig. 2). On the other hand, compounds **3**, **7**, **12**, **15,** and **16** show $^3J_{4\text{-}5}$ values of 3.0, 6.4, 3.0, 2.1, 6.0 Hz, typical of *gauche*-equatorial protons (H-4a in compound **16**, Fig. 2). Moreover in this second series of compounds the chemical shift for proton H-4a$_{eq}$ is downshifted with respect to the signal of the corresponding diastereomers with H-4b in an axial position.

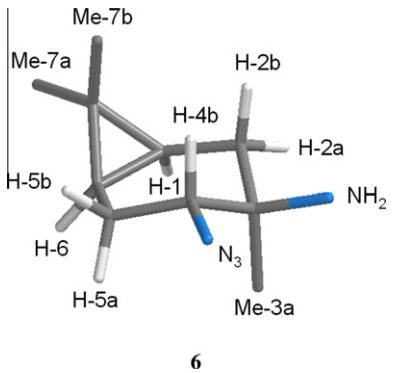


Figure 3. Exemplified representation of the more stable conformation of azido amine **6** (minimized at the semiempirical PM3 level[14]).

Opening of aziridine **5** by sodium azide affords two regioisomeric azido amines **6** and **7**, and the attribution of their configuration was made after the ^{1}H NMR signals were assigned on the basis of COSY, HSAC, and NOESY experiments. The configuration of the major product **6** was attributed on the basis of the NOESY and coupling constants. A NOESY experiment on **6** confirmed the attribution, because when H-4b was irradiated, correlations were observed with H-2b, H-5b, and Me-7b (0.95 ppm). In addition a correlation between the Me-7a (0.99 ppm) and H-1, H-6 protons was observed (Fig. 3).

4. Conclusion

Two new diamine diastereoisomers **8** and **16**, derived from carene were prepared selectively following two separate synthetic routes, that start respectively from 3,4-α-carene oxide **2** and 3,4-β-carene oxide **10**. The synthetic sequence is diastereoselective and in one step also diastereoconvergent. All the passages in the synthetic routes are simple without using complex procedures or expensive reagents. Generally the yields are good, with the exception of the aziridine ring opening. The configuration of the final diamines and of novel intermediates was attributed through ^{1}H NMR spectra observation correlated with conformational analysis and supported by molecular modeling. This is a convenient way to obtain stereoselectively, and from a natural homochiral starting material, new enantiopure vicinal diamines with a *trans*-1,2-diaminocyclohexane skeleton, that can be used as ligands in asymmetric catalytic synthesis.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and

were calibrated using residual undeuterated solvents as the internal reference. Coupling constants (*J*) are given in Hertz. IR spectra were recorded using FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20 °C. All melting points were uncorrected. All reagents were commercially available, were purchased at the highest quality, and were purified by distillation when necessary.

5.2. Procedures and data

5.2.1. Synthesis of (1*S*,3*S*,4*R*,6*R*)-3,4-epoxy-3,7,7-trimethylbicyclo-[4.1.0]heptane 2

A solution of (+)-3-carene **1** (1.51 g, 90% pure, 10 mmol) in chloroform (1.5 mL) was cooled at 0 °C. *m*-Chloroperbenzoic acid (2.46 g, 77% pure, 11 mmol) in chloroform (7 mL) was added to the solution in aliquots over 75 min. After complete addition, stirring was continued at room temperature for 1 h. The progress of the reaction was followed by GC until the starting material was completely consumed. The excess of *m*-chloroperbenzoic acid was destroyed by slow addition of sodium sulfite (10%). After extraction, the organic layer was washed with sodium hydroxide (10% aqueous solution), then with brine and after separation it was dried over Na_2SO_4. The solvent was removed and the residue distilled under reduced pressure to obtain **2** as a colorless oil (1.22 g *Y* = 80%). Obtained spectroscopic data are confirmed by the literature.[29]

5.2.2. Synthesis of (1*S*,3*S*,4*S*,6*R*)-4-azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 3 and (1*R*,3*R*,4*R*,6*S*)-4-azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 4

Products **3** (*Y* = 22%) and **4** (*Y* = 27%) were prepared according to Ref. 12. The spectroscopic data obtained are confirmed by the literature.[30]

5.2.3. Selective synthesis of (1*R*,3*R*,4*R*,6*S*)-4-azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 4

At first, α-carene oxide **2** (0.381 g, 2.5 mmol) was added to a aqueous solution of NaN_3 and acetic acid (0.823 g, 12.5 mmol of NaN_3 in 4 mL of water and 2.3 mL of glacial acetic acid). The heterogeneous mixture was stirred for 48 h at 30 °C and followed by GC. At the end of the reaction, the mixture was treated with DCM and the excess of acetic acid was neutralized with NaOH (10%). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to give the crude azido-alcohol **4** which was purified by column chromatography (cyclohexane/AcOEt 95:5), giving 0.295 g of a white crystalline solid. *Y* = 65%. Obtained spectroscopic data are confirmed by the literature.[33,34]

5.2.4. Synthesis of (1*S*,3*R*,4*S*,6*R*)-3,4-aza-3,7,7-trimethylbicyclo-[4.1.0]-heptane 5

The azido-alcohol **4** (0.576 g, 2.95 mmol) and triphenylphosphine (0.928 g, 3.54 mmol) were dissolved in dioxane (4 mL). The mixture was heated at reflux for 24 h. The reaction was followed by GC. The solvent was removed in vacuo and the resulting crude was diluted with DCM. The solution was washed with citric acid (0.744 g, 10% aqueous solution, 3.54 mmol) then the organic layer was washed with Na_2CO_3 (0.450 g, 10% aqueous solution, 4.25 mmol), dried over Na_2SO_4, and concentrated under reduced pressure to give **5** as a colorless oil (0.428 g, *Y* = 96%); $[\alpha]_D^{20} = +42.7$ (*c* 0.31, $CHCl_3$); ν_{max} (liquid film): 3264, 1460, 1368, 1301, 821 cm^{-1}; NMR ($CDCl_3$): δ_H 0.54–0.66 (m, 3H), 0.73 (dd, 1H, *J* = 14.8, 7.2 Hz), 0.80 (s, 3H), 0.87 (br s, 1H), 0.94 (s, 3H), 1.27 (s, 3H), 1.90 (dd, 1H, *J* = 7.6, 4.8 Hz, H-4a), 1.97 (dd, 1H, *J* = 15.2, 5.2 Hz), 2.25 (m, 1H); δ_C 14.9, 20.0, 21.1, 21.3, 21.9, 26.7, 27.2, 28.7, 35.8, 38.2. Anal. Calcd for $C_{10}H_{17}N$, MW 151.249: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.55; H, 11.18; N, 9.15.

5.2.5. Synthesis of (1*S*,3*R*,4*R*,6*R*)-4-azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 6 and (1*R*,3*S*,4*S*,6*S*)-4-azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 7

To a solution of aziridine **5** (0.458 g, 3.03 mmol) in CH_3CN/H_2O 5:1 (5.5 mL) was added NaN_3 (0.236 g, 3.64 mmol) and $CeCl_3{\cdot}7H_2O$ (0.559 g, 1.51 mmol) and then heated at reflux for 3 h. The reaction was monitored by GC. After cooling, the reaction mixture was concentrated in vacuo to remove the solvent. The crude was diluted with DCM and to the resulting mixture was added Na_2SO_4. The azido-amines **6** and **7** were separated by column chromatography (cyclohexane/AcOEt 50:50) to obtain 0.212 g of **6** (*Y* = 36%) and 5 mg of **7** (*Y* = 1%), both as yellow oils.

5.2.5.1. (1*S*,3*R*,4*R*,6*R*)-4-Azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 6. Yellow oil; $[\alpha]_D^{20} = -40.5$ (*c* 0.31, $CHCl_3$); ν_{max} (liquid film): 3358, 2101, 1589, 1271, 1146, 1124, 812 cm^{-1}; NMR ($CDCl_3$): δ_H 0.68–0.76 (m, 2H, H-1, H-6), 0.95 (s, 3H, Me-7b), 0.99 (s, 3H, Me-7a), 1.05 (s, 3H, Me-3a), 1.10 (dd, 1H, *J* = 14.1, 3.8 Hz, H-2b), 1.43 (br s, 2H, NH_2), 1.78 (ddd, 1H, *J* = 14.5, 10.7, 8.1 Hz, H-5a), 1.86 (dd, 1H, *J* = 14.1, 9.8 Hz, H-2a), 2.12 (dd, 1H, *J* = 14.5, 7.3 Hz, H-5b), 3.03 (dd, 1H, *J* = 10.7, 7.7 Hz, H-4b); δ_C 15.9, 17.9, 19.3, 20.3, 21.2, 25.0, 28.8, 34.8, 51.8, 69.1. Anal. Calcd for $C_{10}H_{18}N_4$, MW 194.277: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.79; H, 9.48; N, 28.72.

5.2.5.2. (1*R*,3*S*,4*S*,6*S*)-4-Azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 7. Yellow oil; $[\alpha]_D^{20} = +37.7$ (*c* 0.28, $CHCl_3$); ν_{max} (liquid film): 3346, 2105, 1388, 1248, 1108, 799 cm^{-1}; NMR ($CDCl_3$): δ_H 0.67–0.77 (m, 2H, H-1, H-6), 1.01 (s, 3H), 1.03 (s, 3H), 1.17–1.34 (m, 2H), 1.28 (s, 3H), 2.02 (dd, 1H, *J* = 15.0, 8.1 Hz), 2.16 (ddd, 1H, *J* = 15.0, 8.5, 6.0 Hz, H-5), 2.97 (dd, 1H, *J* = 8.5, 6.4 Hz, H-4), 3.40 (br s, 2H); δ_C 15.4, 18.5, 18.7, 20.6, 22.4, 25.8, 28.5, 29.7, 54.0, 64.3. Anal. Calcd for $C_{10}H_{18}N_4$, MW 194.277: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.94; H, 9.52; N, 28.91.

5.2.6. Synthesis of (1*S*,3*R*,4*R*,6*R*)-3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diamine 8

The azido-amine **6** (0.212 g, 1.09 mmol) was dissolved in anhydrous MTBE (2 mL) and stirred at 0 °C in an ice-water bath. The solution was treated with $LiAlH_4$ (0.05 g, 1.31 mmol). The reaction was stirred for 4 h until it reached room temperature. The reaction was monitored by GC. The excess of $LiAlH_4$ was eliminated with H_2O. The mixture was dried with Na_2SO_4, filtered, washed with DCM, and evaporated in vacuo to give the diamine **8** (0.185 g, *Y* = 99%) as a colorless oil: $[\alpha]_D^{20} = -12.3$ (*c* 0.29, $CHCl_3$); ν_{max} (liquid film): 3281,1586, 1376, 1146, 810 cm^{-1}; NMR ($CDCl_3$): δ_H 0.63 (t, 1H, *J* = 9.0 Hz, H-6), 0.68 (td, 1H, *J* = 9.4, 4.7 Hz, H-1), 0.94 (s, 3H, Me), 0.96 (s, 3H, Me), 1.00 (s, 3H, Me), 1.07 (dd, 1H, *J* = 14.5, 4.7 Hz, H-2b), 1.27 (br s, 4H, 2 NH_2), 1.40 (ddd, 1H, *J* = 14.5, 11.1, 7.7 Hz, H-5a), 1.86 (dd, 1H, *J* = 14.1, 9.4 Hz, H-2a), 2.00 (dd, 1H, *J* = 14.5, 6.8 Hz, H-5b), 2.25 (dd, 1H, *J* = 11.1, 6.8 Hz, H-4b); δ_C 15.7, 17.7, 19.3, 20.0, 20.9, 29.0, 29.3, 36.3, 52.2, 56.1. Anal. Calcd for $C_{10}H_{20}N_2$, MW 168.279: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.25; H, 12.15; N, 16.63.

5.2.7. Synthesis of (1*S*,3*R*,4*R*,6*R*)-4-iodo-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 9

(+)-3-Carene **1** (2.22 g, 90% pure, 14.68 mmol) and NaI (2.20 g, 14.68 mmol) were dissolved in THF/H_2O (50 mL, 7:3). The mixture was cooled in an ice-water bath and stirred; H_2SO_4 (8.64 g, 88.08 mmol) was then added dropwise. After complete addition H_2O_2 was added dropwise (3.88 mL, 35% aqueous solution, 44.04 mmol). An exothermic reaction and development of a dark red color in the reaction mixture were observed. After complete addition, stirring was continued at room temperature until the solution turned colorless (about 12 h). The progress of the reaction

was followed by GC. THF was then removed under vacuo. The resulting mixture was treated with $Na_2S_2O_3$ (4.58 g, 5% aqueous solution, 29 mmol) and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography with cyclohexane/AcOEt (97:3) to give a brown oil (3.39 g, 12.11 mmol, *Y* = 82%). Obtained spectroscopic data are confirmed by the literature.[36]

5.2.8. Synthesis of (1*S*,3*R*,4*S*,6*R*)-3,4-epoxy-3,7,7-trimethylbicyclo-[4.1.0]heptane 10

A solution of **9** (1.581 g, 5.6 mmol) in THF/Et_2O (25 mL, 1:1) anhydrous under an N_2 atmosphere was stirred at room temperature. The solution was treated with NaH (0.176 g, 7.3 mmol). The progress of the reaction was followed by GC. After 5.5 h the reaction was complete. The excess NaH was destroyed with cold water added dropwise. The mixture was extracted with DCM and washed with brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified over column chromatography with cyclohexane/AcOEt (97:3) to give **10** as a colorless oil (0.714 g, 4.7 mmol, *Y* = 84%). Spectral data obtained are confirmed by the literature. ^{1}H NMR ($CDCl_3$): δ_H 0.51 (td, 1H, *J* = 8.1, 2.1 Hz), 0.55 (td, 1H, *J* = 7.7, 2.1 Hz), 0.91 (s, 3H), 0.95 (s, 3H), 1.29 (s, 3H), 1.76 (d, 1H, *J* = 16.6 Hz), 1.77 (d, 1H, *J* = 15.7 Hz), 2.05 (dd, 1H, *J* = 16.6, 9.0 Hz, H-2), 2.26 (ddd, 1H, *J* = 15.7, 9.0, 5.5 Hz, H-5); 2.86 (d, 1H, *J* = 5.5 Hz, H-4).

5.2.9. Synthesis of (1*S*,3*R*,4*R*,6*R*)-4-azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 11 and (1*R*,3*S*,4*S*,6*S*)-4-azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 12

A solution of β-carene oxide **10** (0.300 g, 1.97 mmol) in methanol was mixed with NaN_3 (0.275 g, 3.95 mmol) and NH_4Cl (0.105 g, 1.97 mmol). The resulting mixture was heated at reflux for 14 h. The reaction was monitored by GC. The mixture was allowed to cool to room temperature, and the solvent was removed in vacuo. The resulting mixture was diluted with DCM and filtered on Na_2SO_4. The azido-alcohols **11** and **12** were separated by silica gel column chromatography with cyclohexane/AcOEt (95:5) to give **11** (0.142 g, *Y* = 36%) and **12** (0.141 g, *Y* = 36%) as yellow oils. Obtained spectroscopic data are confirmed by the literature.[30]

5.2.9.1. (1*S*,3*R*,4*R*,6*R*)-4-Azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 11. Yellow oil, $[\alpha]_D^{20} = -26.2$ (*c* 0.20, $CHCl_3$), ν_{max} (liquid film): 3430, 2104, 1255, 1117, 1007, 946 cm^{-1}; NMR ($CDCl_3$): δ_H 0.66 (t, 1H, *J* = 8.5 Hz, H-6), 0.75 (td, 1H, *J* = 9.0, 5.1 Hz, H-1), 0.98 (s, 6H), 1.20 (s, 3H), 1.27 (ddd, 1H, *J* = 9.8, 4.7, 0.8 Hz, H-2b), 1.75 (ddd, 1H, *J* = 14.5, 11.1, 8.1 Hz, H-5a), 1.94 (br s, 1H), 1.98 (dd, 1H, *J* = 14.5, 9.8 Hz, H-2a), 2.14 (dd, 1H, *J* = 14.5, 7.3 Hz, H-5b), 3.21 (dd, 1H, *J* = 11.1, 7.3 Hz, H-4b); δ_C 15.9, 19.9, 20.0, 20.7, 25.6, 26.4, 28.8, 33.7, 67.4, 72.8. Anal. Calcd for $C_{10}H_{17}N_3O$, MW 195.261: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.37; H, 8.82; N, 21.68.

5.2.9.2. (1*R*,3*S*,4*S*,6*S*)-4-Azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-ol 12. Yellow oil, $[\alpha]_D^{20} = +93.4$ (*c* 0.31, $CHCl_3$), ν_{max} (liquid film): 3467, 2106, 1376, 1258, 1049, 824 cm^{-1}; NMR ($CDCl_3$): δ_H 0.61 (td, 1H, *J* = 9.4, 3.0 Hz, H-6), 0.72 (td, 1H, *J* = 9.4, 6.0 Hz, H-1), 1.02 (s, 3H), 1.04 (s, 3H), 1.27 (s, 3H), 1.36 (dd, 1H, *J* = 15.4, 6.4 Hz, H-2b), 1.42 (dt, 1H, *J* = 15.8, 3.0 Hz, H-5a), 1.47 (br s, 1H), 1.89 (ddd, 1H, *J* = 15.8, 9.0, 0.9 Hz, H-2a), 2.29 (ddd, 1H, *J* = 15.8, 9.0, 6.8 Hz, H-5b), 3.56 (dd, 1H, *J* = 6.8, 3.0 Hz, H-4a); δ_C 15.2, 18.1, 18.4, 18.7, 22.8, 26.4, 26.5, 28.9, 63.5, 70.3. Anal. Calcd for $C_{10}H_{17}N_3O$, MW 195.261: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.42; H, 8.55; N, 21.70.

5.2.10. Synthesis of (1*S*,3*S*,4*R*,6*R*)-3,4-aza-3,7,7-trimethylbicyclo-[4.1.0]heptane 13

From azido-alcohol **11**: a solution of **11** (0.060 g, 0.31 mmol) in dioxane (1 mL) was poured into a round bottomed flask equipped with magnetic stirring and mixed at room temperature with triphenylphosphine (0.097 g, 0.37 mmol) for 24 h. The reaction was followed by GC. The solvent was removed in vacuo and the resulting crude was diluted with DCM. The solution was washed with citric acid (0.078 g, 10% aqueous solution, 0.37 mmol), then, the organic layer was washed with Na_2CO_3 (0.047 g, 10% aqueous solution, 0.45 mmol), dried over Na_2SO_4 and concentrated under reduced pressure to give **13** as a colorless oil (0.047 g, *Y* = 79%).

From azido-alcohol **12**: a solution of **12** (0.127 g, 0.65 mmol) in dioxane (2 mL) was stirred and heated at reflux with triphenylphosphine (0.205 g, 0.78 mmol) for 36 h. The reaction was followed by GC. The solvent was removed in vacuo and the resulting crude was diluted with DCM. The solution was washed with citric acid (0.164 g, 10% aqueous solution, 0.78 mmol), then, the organic layer was washed with Na_2CO_3 (0.099 g, 10% aqueous solution, 0.94 mmol), dried over Na_2SO_4 and concentrated under reduced pressure to give **13** as colorless oil (0.063 mg, *Y* = 64%): $[\alpha]_D^{20} = +21.0$ (*c* 0.40, $CHCl_3$); ν_{max} (liquid film): 3256, 1306, 1270, 1205, 1164, 1136, 1074, 920, 825 cm^{-1}; NMR ($CDCl_3$): δ_H 0.31 (td, 1H, *J* = 9.0, 3.4 Hz, H-6), 0.42 (td, 1H, *J* = 9.0, 3.8 Hz, H-1), 0.71 (s, 3H), 0.98 (s, 3H), 1.10 (s, 3H), 1.24 (br s, 1H), 1.31 (dd, 1H, *J* = 15.4, 3.4 Hz, H-2b), 1.52 (dt, 1H, *J* = 15.8, 3.0 Hz, H-5b), 1.70 (t, 1H, *J* = 2.6 Hz, H-4b), 1.99 (dd, 1H, *J* = 15.4, 9.4 Hz, H-2a), 2.13 (ddd, 1H, *J* = 15.8, 9.4, 2.1 Hz, H-5a); δ_C 13.0, 14.9, 15.7, 16.5, 18.2, 23.3, 25.0, 28.0, 36.7, 72.8. Anal. Calcd for $C_{10}H_{17}N$, MW 151.249: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.25; H, 11.46; N, 9.37.

5.2.11. Synthesis of (1*R*,3*R*,4*R*,6*S*)-4-azido-4,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 14 and (1*S*,3*S*,4*S*,6*R*)-4-azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 15

To a solution of aziridine **13** (0.329 g, 2.18 mmol) in CH_3CN/H_2O 5:1 (4.4 mL) was added NaN_3 (0.170 g, 2.61 mmol) and $CeCl_3{\cdot}7H_2O$ (0.406 g, 1.09 mmol) and heated at reflux for 45 min. The reaction was monitored by GC. After cooling, the reaction mixture was concentrated in vacuo to remove the solvent. The crude was diluted with DCM and to the mixture resulting was added Na_2SO_4. The solution was filtered on Na_2SO_4. The azido-amines **14** and **15** were separated on column chromatography (cyclohexane/AcOEt 10:90) to obtain 0.131 g of **14** (*Y* = 31%) as a yellow oil and 0.284 g of **15** (*Y* = 67%) as a white solid.

5.2.11.1. (1*R*,3*R*,4*R*,6*S*)-4-Azido-4,7,7-trimethylbicyclo[4.1.0]-heptan-3-amine 14. Yellow oil, $[\alpha]_D^{20} = -74.2$ (*c* 0.21, $CHCl_3$), ν_{max} (liquid film): 3323, 2096, 1378, 1256, 1099, 805, 770 cm^{-1}; NMR ($CDCl_3$): δ_H 0.64 (t, 1H, *J* = 8.1 Hz, H-6), 0.72 (td, 1H, *J* = 9.8, 4.7 Hz, H-1), 0.95 (s, 3H), 0.98 (s, 3H), 1.18 (br s, 2H), 1.23 (s, 3H), 1.30 (dd, 1H, *J* = 14.1, 4.7 Hz, H-2b), 1.42 (ddd, 1H, *J* = 14.7, 11.5, 8.1 Hz, H-5a), 2.00 (dd, 1H, *J* = 14.7, 6.8 Hz, H-5b), 2.08 (dd, 1H, *J* = 14.1, 9.8 Hz, H-2a), 2.43 (dd, 1H, *J* = 11.5, 7.3 Hz, H-4b); δ_C 15.1, 15.7, 18.2, 19.2, 20.4, 28.0, 28.9, 31.8, 54.1, 65.7. Anal. Calcd for $C_{10}H_{18}N_4$, MW 194.277: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.64; H, 9.25; N, 28.68.

5.2.11.2. (1*S*,3*S*,4*S*,6*R*)-4-Azido-3,7,7-trimethylbicyclo[4.1.0]heptan-3-amine 15. Crystals mp 50–54 °C, $[\alpha]_D^{20} = +138.8$ (*c* 0.27, $CHCl_3$), ν_{max} (Nujol): 3388, 2098, 1607, 1269, 1008, 805, 773 cm^{-1}; NMR ($CDCl_3$): δ_H 0.56 (td, 1H, *J* = 9.0, 2.1 Hz, H-6), 0.71 (td, 1H, *J* = 9.4, 6.4 Hz H-1), 1.01 (s, 3H), 1.03 (s, 3H), 1.08 (s, 3H), 1.18 (dd, 1H, *J* = 15.0, 6.0 Hz, H-2b), 1.34 (br s, 2H), 1.54 (ddd, 1H, *J* = 15.0, 9.8, 1.3 Hz, H-2a), 1.66 (dt, 1H, *J* = 14.1, 2.1 Hz, H-5a), 2.36 (ddd, 1H, *J* = 16.2, 9.0, 7.7 Hz, H-5b), 3.23 (dt, 1H, *J* = 7.7, 2.1 Hz, H-4a); δ_C 15.2, 17.1, 18.4, 18.5, 22.3, 27.4, 28.9, 29.1, 50.6,

66.0. Anal. Calcd for $C_{10}H_{18}N_4$, MW 194.277: C, 61.82; H, 9.34; N, 28.84. Found: C, 61.95; H, 9.28; N, 28.77.

5.2.12. Synthesis of (1*S*,3*R*,4*R*,6*R*)-3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diamine 8

The azido-amine **14** (0.129 g, 0.66 mmol) was dissolved in anhydrous MTBE (1 mL) and stirred at 0 °C in an ice-water bath. The solution was treated with $LiAlH_4$ (0.033 g, 0.86 mmol). The reaction was stirred for 20 min until room temperature was reached. The reaction was monitored by GC. The excess of $LiAlH_4$ was eliminated with H_2O saturated with Na_2SO_4. The mixture was treated with Na_2SO_4, filtered, washed with DCM, and evaporated under reduced pressure to give the diamine **8** (0.093 g, Y = 85%) as a colorless oil: $[\alpha]_D^{20} = -12.3$ (c 0.29, $CHCl_3$); ν_{max} (liquid film): 3281,1586, 1376, 1146, 810 cm^{-1}; NMR ($CDCl_3$): δ_H 0.63 (t, 1H, J = 9.0 Hz, H-6), 0.68 (td, 1H, J = 9.4, 4.7 Hz, H-1), 0.94 (s, 3H, Me), 0.96 (s, 3H, Me), 1.00 (s, 3H, Me), 1.07 (dd, 1H, J = 14.5, 4.7 Hz, H-2b), 1.27 (br s, 4H, 2 NH_2), 1.40 (ddd, 1H, J = 14.5, 11.1, 7.7 Hz, H-5a), 1.86 (dd, 1H, J = 14.1, 9.4 Hz, H-2a), 2.00 (dd, 1H, J = 14.5, 6.8 Hz, H-5b), 2.25 (dd, 1H, J = 11.1, 6.8 Hz, H-4b); δ_C 15.7, 17.7, 19.3, 20.0, 20.9, 29.0, 29.3, 36.3, 52.2, 56.1. Anal. Calcd for $C_{10}H_{20}N_2$, MW 168.279: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.25; H, 12.15; N, 16.63.

5.2.13. Synthesis of (1*S*,3*S*,4*S*,6*R*)-3,7,7-trimethylbicyclo[4.1.0]heptane-3,4-diamine 16

The azido-amine **15** (0.239 g, 1.23 mmol) was dissolved in anhydrous MTBE (2 mL) and stirred at 0 °C in an ice-water bath. The solution was treated with $LiAlH_4$ (97 mg, 1.60 mmol). The reaction was stirred for 70 min until room temperature was reached. The reaction was monitored by GC. The excess of $LiAlH_4$ was eliminated with H_2O. The mixture was treated with Na_2SO_4, filtered, washed with DCM, and evaporated under vacuo to give the diamine **16** (0.187 g, Y = 91%) as a colorless oil; $[\alpha]_D^{20} = +33.3$ (c 0.47, $CHCl_3$), ν_{max} (liquid film): 3282, 1651, 1574, 1558, 1152 cm^{-1}; NMR ($CDCl_3$): δ_H 0.60 (td, 1H, J = 8.5, 4.7 Hz, H-1), 0.67 (td, 1H, J = 9.4, 6.8 Hz, H-6), 1.00 (ddd, 1H, J = 15.4, 10.2, 5.6 Hz, H-5a), 0.99 (s, 3H), 1.00 (s, 3H), 1.04 (s, 3H), 1.27 (dd, 1H, J = 15.0, 6.4 Hz, H-2b), 1.41 (br s, 4H), 1.54 (dd, 1H, J = 15.0, 8.6 Hz, H-2a), 2.14 (ddd, 1H, J = 15.4, 8.6, 6.8 Hz, H-5b), 2.67 (ddd, 1H, J = 6.8, 6.0, 0.9 Hz, H-4a); δ_C 15.7, 18.1, 18.8, 19.6, 26.4, 26.7, 28.9, 30.6, 51.5, 55.8. Anal. Calcd for $C_{10}H_{20}N_2$, MW 168.279: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.46; H, 12.08; N, 16.72.

Acknowledgments

The financial support of this research by a grant from University of Camerino and from MIUR-PRIN is gratefully acknowledged.

References

1. Fache, F.; Schulz, E.; Tommasino, M.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2232.
2. Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497–526.
3. Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3196.
4. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
5. Arai, S.; Takita, S.; Nishida, A. *Eur. J. Org. Chem.* **2005**, 5262–5267.
6. Saravanan, P.; Bisai, A.; Baktaharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693–4706.
7. Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2566–2571.
8. Chen, X.; Wang, J.; Zhu, Y.; Shang, D.; Gao, B.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *Chem. Eur. J.* **2008**, *14*, 10888–10891.
9. Rasappan, R.; Reiser, O. *Eur. J. Org. Chem.* **2009**, 1305–1308.
10. Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 2124–2126.
11. Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580–591.
12. Liu, W.; Cui, X.; Cun, L.; Zhu, J.; Deng, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2525–2530.
13. Liu, W.; Cui, X.; Cun, L.; Wu, J.; Deng, J.; Fan, Q. *Synlett* **2005**, 1591–1595.
14. Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584–3591.
15. Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745–8747.
16. Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610–2621.
17. Baudouy, R.; Prince, P. *Tetrahedron* **1989**, *45*, 2067–2074.
18. Marron, B. E.; Nicolaou, K. C. *Synthesis* **1989**, 537–539.
19. Tius, M. A.; Kerr, M. A. *Synth. Commun.* **1988**, *18*, 1905–1911.
20. Baker, R.; Borges, M.; Cooke, N. G.; Herbert, R. H. *J. Chem. Soc., Chem. Commun.* **1987**, 414–416.
21. Mori, K.; Kato, M. *Tetrahedron Lett.* **1986**, *27*, 981–982.
22. Watts, C. C.; Thoniyot, P.; Hirayama, L. C.; Romano, T.; Singaram, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1829–1835.
23. Wang, M.-C.; Liu, L.-T.; Zhang, J.-S.; Shi, Y.-Y.; Wang, D.-K. *Tetrahedron: Asymmetry* **2004**, *15*, 3853–3859.
24. Steiner, D.; Sethofer, S. G.; Goralski, C. T.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1477–1483.
25. Xu, Q.; Wu, X.; Pan, X.; Chan, A. C. S.; Yang, T.-K. *Chirality* **2002**, *14*, 28–31.
26. Pu, L.; Hong-Bin, Y. *Chem. Rev.* **2001**, *101*, 757–824.
27. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. pp 255–297.
28. Cimarelli, C.; Fratoni, D.; Palmieri, G. *Tetrahedron: Asymmetry* **2009**, *20*, 2234–2239.
29. Brown, H. C.; Suzuki, A. *J. Am. Chem. Soc.* **1967**, *89*, 1933–1941.
30. Bakaleinik, G. A.; Shagidullin, Rif. R.; Shagidullin, R. R.; Chernova, A. V.; Musin, R. Z.; Karlin, V. V. *Zh. Obshch. Khim.* **1992**, *62*, 655–660. CAN 117:234268.
31. Sommerdijk, N. A. J. M.; Buynsters, P. J. J. A.; Akdemir, H.; Geursts, D. G.; Nolte, R. J. M.; Zwanenburg, B. *J. Org. Chem.* **1997**, *62*, 4955–4960.
32. Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437–472.
33. Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **1999**, *64*, 6094–6096.
34. Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646–650.
35. Kaufmann, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parson, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119–3121.
36. Barluenga, J.; Marco-Arias, M.; González-Bobes, F.; Ballesteros, A.; González, J. M. *Chem. Eur. J.* **2004**, *10*, 1677–1682.
37. Voronkov, M. V.; Gontcharov, A. V.; Kanamarlapudi, R. C.; Richardson, P. F.; Wang, Z.-M. *Org. Process Res. Dev.* **2005**, *9*, 221–224.
38. SPARTAN '06 1.1.1—Wavefunction Inc. 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612.