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Tetrahedron 61 (2005) 1449–1457

Regio- and stereoselective reactions between cyclic Baylis–Hillman type adducts and N-nucleophiles and P-nucleophile

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Received 20 September 2004; revised 8 November 2004; accepted 2 December 2004

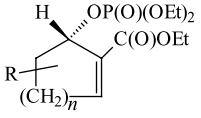
Available online 16 December 2004

Abstract—New important organic compounds multifunctionalized cyclic 6-membered and 7-membered allylic amines, azide and phosphonates have been obtained via regio- and diastereoselective reactions of cyclic Baylis–Hillman type adducts **1** with N-nucleophiles and P-nucleophile. We have found that the reactions proceed by S_N2 or S_N2' processes exclusively, or by both processes simultaneously. The S_N2' process occurs with *anti* stereochemistry.

1. Introduction

Baylis–Hillman acyclic adducts are versatile multifunctional molecules. They have proved useful synthetic intermediates[1] and undergo a variety of organic transformations with regio- and stereochemical control.[2] Several successful examples of such transformations have already been reported, including synthesis of allylic amino compounds.[3] But little work has been described on cyclic Baylis–Hillman adducts. They are mainly connected with addition reactions of metalloorganic reagents.[4]

We have previously reported the synthesis of novel cyclic Baylis–Hillman type adducts **1** of defined stereochemistry (Fig. 1).[5]



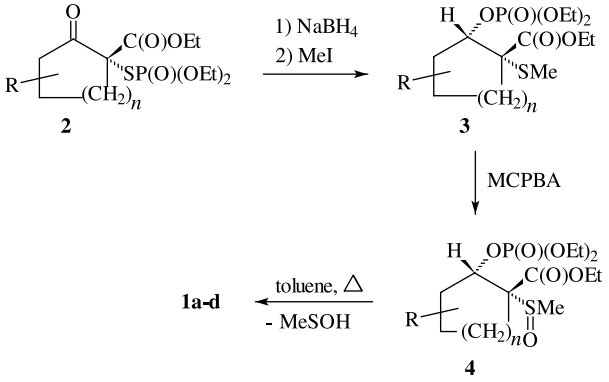
1a n = 2, R = H
1b n = 3, R = H
1c n = 2, R = 5-Me
1d n = 2, R = 3-Ph

Figure 1.

In continuation of our interest in the synthesis of multifunctional cyclic compounds, we have studied regio- and stereoselectivity of the reaction of adducts **1** with nucleophiles. They lead to functionalized 6 and 7-membered ring allylic amines, allylic azide and allylic phosphonates of defined stereochemistry.

2. Results and discussion

Our synthetic approach to Baylis–Hillman type adducts **1** involves reduction of the carbonyl group in readily available thiophosphates **2**[5] by $NaBH_4$ in the presence of MeI, subsequent oxidation of intermediate **3** to sulphoxide **4** and *cis* elimination from the latter (Scheme 1).



Scheme 1.

Initially we studied the reactions between adducts **1a** and **1b** with different amines, sodium azide and trimethyl phosphite. Treatment of **1a** with benzylamine and diethylamine at room temperature furnished the corresponding secondary

Keywords: Baylis–Hillman type adducts; Multifunctionalized allylic compounds; S_N2' reaction; Stereochemistry.
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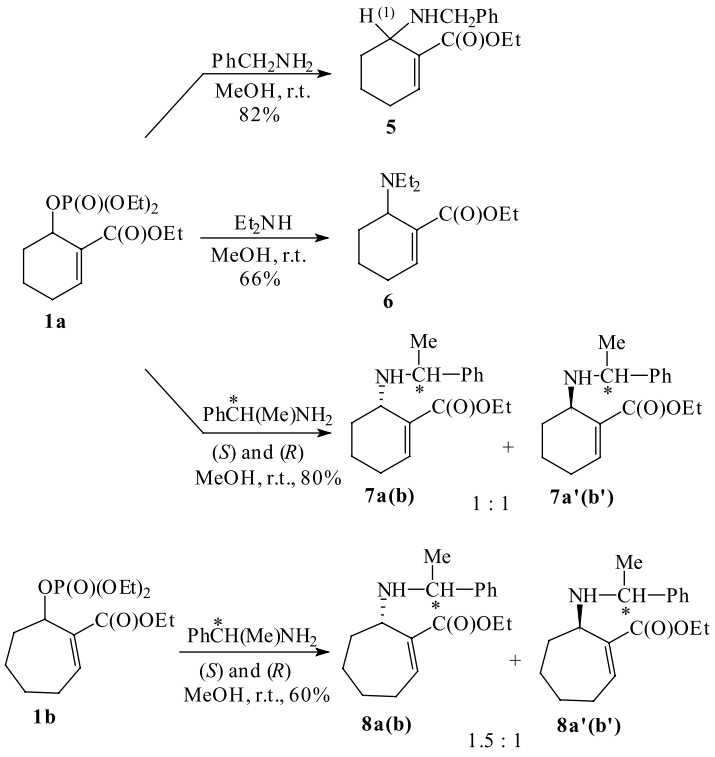
doi:10.1016/j.tet.2004.12.008



Scheme 2.

5 and tertiary cyclic allylic amines **6** in good yield (82% and 66%, respectively). Reaction of **1a** and **1b** with optically active *S*-(−)-α-methylbenzylamine and *R*-(+)-α-methylbenzylamine in methanol under the same reaction conditions provided 6-membered cyclic amines **7a**(**b**) in 80% yield and 7-membered cyclic amines **8a**(**b**) in 60% yield, as a mixture of two diastereoisomers in the ratio 1:1 and 1.5:1, respectively (Scheme 2).

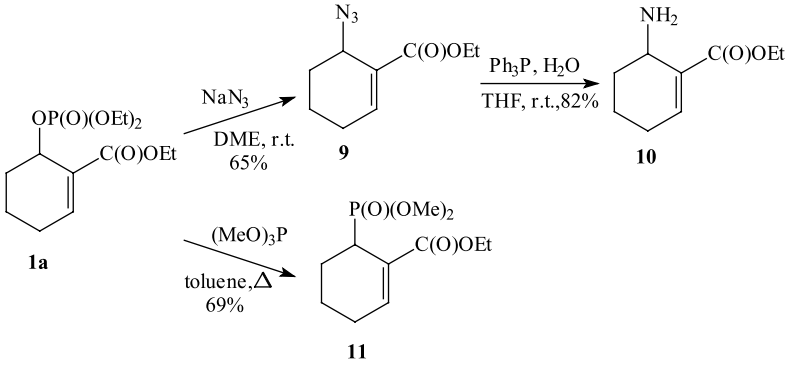
Reaction of **1a** with sodium azide in DME solution at room temperature afforded a new allylic azide **9** in good yield. Reduction of azide **9** under standard conditions with $Ph_3P/THF/H_2O$[3b] gave exclusively the primary allylic amine **10**. The phosphate **1a** was also subjected to reaction with trimethyl phosphite in boiling toluene, providing phosphonate **11** in 69% yield (Scheme 3).

The structure of the amines, azide and phosphonate obtained was confirmed by ^1H NMR analysis and mass spectrometry.

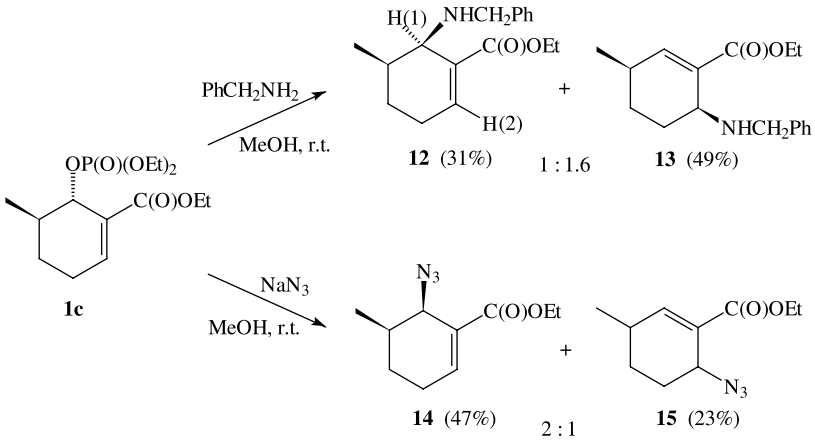
The quasiequatorial position of allylic hydrogen ($H^{(1)}$) in **5** was determined on the basis of characteristic vicinal coupling constants $^3J_{HaHe'}=3.8$ Hz, $^3J_{HeHe'}=3.8$ Hz.[6] Determination of the structures of amines **6**, **7a(b)** and **8a(b)** was impossible, they exhibited allylic protons peaks at 3.75, 3.66, and 3.91 ppm as multiplets. Configuration of amines **7** was determined by hydrogenolysis, which afforded of 2-amino-cyclohexanecarboxylic acid ethyl ester of known configuration.[7]

2.1. Regio- and stereoselectivity of reactions between adducts 1c,d and N-nucleophiles and P-nucleophile

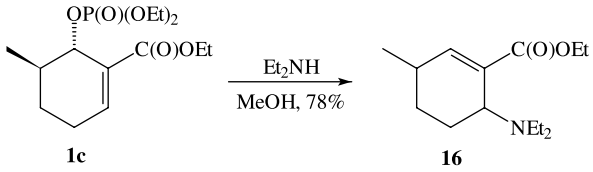
Yamamoto et al. reported that phosphate ester is an excellent leaving group in S_N2' selective reactions between organocopper reagents and acyclic allylic alcohol derivatives.[8] These authors have also found that acyclic allylic phosphates gave, with Grignard reagents and in the presence



Scheme 3.



Scheme 4.



Scheme 5.

of an iron catalyst, cross-coupling products with high S_N2 selectivity.[9]

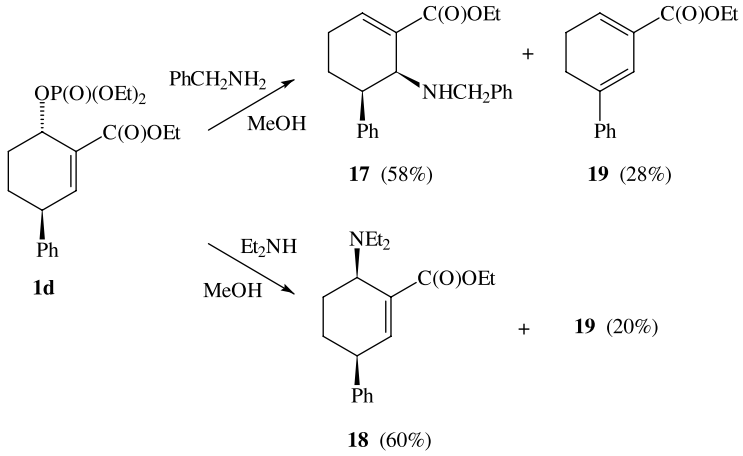
Therefore, it was of interest to test the regio- and stereoselectivity of reactions of adducts **1c** and **1d** (which are functionalized allylic phosphates) containing an additional alkyl or aryl substituent in the ring, with nucleophiles. Nucleophilic attack may follow an S_N2 or S_N2' pathway, or both pathways simultaneously. The stereochemical course of the S_N2' reaction, of crucial importance in synthesis, is clear in many instance but much less clear in others. In many cases entering and leaving groups departed from the same side of the C=C plane.[10] However, there are several experiments which show that the *anti* mode is also possible.[11] The factors which favor the *anti* mode are not yet completely understood, but there appears to be no doubt that stereoelectronic effects play an important role in these reactions.[12]

We have found that in the reaction of **1c** with benzylamine and sodium azide both processes (S_N2 and S_N2') operated, giving the mixture of regioisomers **12** and **13**, and **14** and **15** in the ratio 1:1.6 and 2:1, respectively (Scheme 4). The S_N2 and S_N2' product distribution of these reactions is not solvent dependent.[13] In polar solvents like methanol, as well as in much less polar solvents like DME, a similar ratio of final products was observed. The resulting regioisomers could be easily separated by silica gel chromatography.

In contrast, reaction of **1c** with diethylamine performed in methanol at r.t. is fully regio- and diastereoselective providing one regioisomer **16** (S_N2' product) in high yield (Scheme 5).

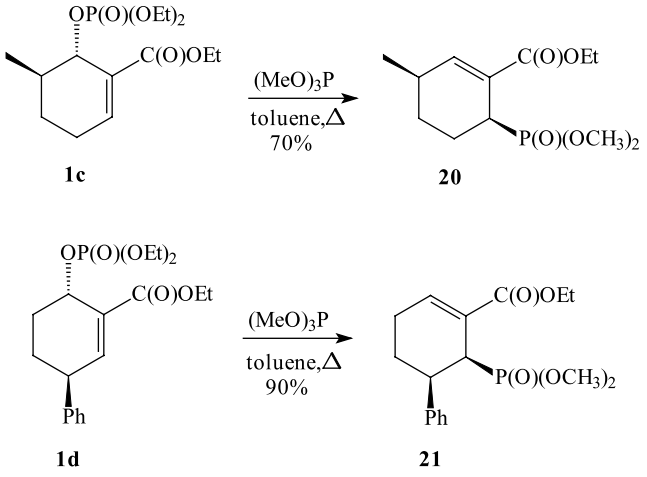
The extension of our investigation to the reactions of adduct **1d** with N-nucleophiles has shown that, with benzylamine and diethylamine alongside amounts of cyclic conjugated diene **19**,[14] allylic amine **17** (S_N2' product) and allylic amine **18** (S_N2 product) were formed (Scheme 6).

Reactions between adducts **1c** and **1d** with P-nucleophile such as trimethylphosphite lead to one regioisomer of the



Scheme 6.

corresponding novel allylic phosphonate **20** in 70% yield and allylic phosphonate **21** in 90% yield, exclusively (Scheme 7).



Scheme 7.

Reactions presented in Scheme 4 are partially regioselective giving products via S_N2 and S_N2' processes, whereas reactions presented in Schemes 5–7 are fully regioselective providing allylic amines **16**, **17** and allylic phosphonates **20**, **21** via an S_N2' process. It is difficult to explain unambiguously the observed different regioselectivity in the investigated reactions. However, it is very likely that reactions of **1c** with diethylamine, benzylamine and azide are controlled by the following factors: the nature of nucleophile, conformational equilibrium in the starting material and the steric hindrance of the methyl group in the transition states of the competing S_N2 and S_N2' reaction pathways. The ratio of regioisomers was established by ^1H NMR. The structure and configuration of compounds prepared were determined on the basis of ^1H, ^{13}C NMR (including COSY experiments), in particular characteristic values of vicinal H–H coupling constants: $J_{ae'}$ and $J_{ee'}$, vicinal ^{31}P–^{13}C coupling constants values, and in some cases (for **17**, **20** and **21**) were confirmed by the data obtained from calculations performed with the AM-1 program.[15] The values of the vicinal coupling constants between axial–quasiaxial protons are generally higher than these for an axial–quasiequatorial orientation.[6] The values of coupling constants observed also revealed a *cis* relationship between the methyl (phenyl) substituent and functional groups in **12**, **13**, **14**, **17**, **18**, **20** and **21**. Karplus-like dependence of vicinal ^{31}P–^{13}C coupling on the dihedral angle has been established for the $(MeO)_2P(O)$ group.[16] The small values of $^3J_{C(4)P}$ observed for compounds **11**, **20** and **21**, indicated a quasiaxial orientation for the phosphonate group.[17]

It was not possible to determine *syn* or *anti* stereochemistry of S_N2' process for all products obtained. However, it seems reasonable, on the basis of presented NMR data, to assume that nucleophilic attack of benzylamine, azide anion and trimethyl phosphite on the allylic system of adducts **1c** and **1d** is *anti* to the leaving phosphate group via a chairlike transition state. A non-concerted S_N2' process is not excluded. In such cases *anti* attack of the nucleophile creates an anion stabilized by the presence of a carboester group in the α-position. The next step should involve elimination of phosphoric acid with formation of the final product. We excluded the possibility of allylic rearrangement of adducts **1** under reaction conditions, which consequently provided a final product with *anti* stereochemistry.[11a,18]

3. Conclusion

Reactions of cyclic Baylis–Hillman type adducts **1** with nucleophiles presented here constitute an excellent route to novel synthetically important compounds: sterically defined 6-membered and 7-membered cyclic multifunctional allylic amines, azide and phosphonates. The results constitute new examples of S_N2' reactions proceeding with *anti* stereochemistry. The whole spectrum, from *syn* to *anti*, is to be expected depending mainly in any particular case, on the nature of displacing and displaced groups.

4. Experimental

4.1. General

^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200.13, 50.32 and 81.02 MHz, respectively (using deuterochloroform as solvent) unless otherwise noted IR spectra were measured on an Ati Mattson Infinity FT IR 60. GC spectra were performed on a Hewlett-Packard 5890. MS spectra (EI, CI, and HRMS) were recorded on a Finnigan MAT 95 spectrometer. Optical rotation values were measured in 100 mm cell on Perkin Elmer 241 MC under Na lamp radiation.

All the reactions were carried out using anhydrous conditions and under an atmosphere of argon. Chromatographic purification was performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with indicated eluent. Chemicals and solvents were obtained from commercial sources and distilled or dried according to standard methods. All phosphates, i.e. 6-(diethoxy-phosphoryloxy)-cyclohex-1-enecarboxylic acid ethyl ester (**1a**) were prepared as described.[5]

4.2. Synthesis of allylic amines 5, 6, 7a,a′, 7b,b′, 8a,a′ 8b,b′, 12, 13, 16, 17, 18 and allylic azides 9, 14, 15

General procedure. To a solution of appropriate allylic phosphates (0.3 mmol) in dry methanol (5 mL) or, in the case of azide, in dry dimethoxyethane (5 mL), 0.6 mmol of amines or azide was added at room temperature under argon. Progress of the reaction was monitored by TLC chromatography. When the reaction was complete (24 h for amines and three days for azide), solvent was removed in vacuo, residue was diluted water and extracted with ether (3×5 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed to leave colorless oils, which were purified by silica gel chromatography (petroleum ether/EtOAc).

4.2.1. 6-Benzyloamino-cyclohex-1-enecarboxylic acid ethyl ester (5). R_f (ethyl acetate/petroleum ether 1:1)=0.46. Yield: 82% (63.7 mg from 92.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.35–1.67 (m, 2H, CH_2), 1.72–1.95 (m, 2H, CH_2), 1.82 (s, 1H, NH), 2.10–2.38 (m, 2H, CH_2), 3.63 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CHNH), 3.82 (AB, $^2J_{HH}$=12.8 Hz, 2H, $NHCH_2$), 4.18 (q, $^3J_{HH}$=7.1 Hz, 2H, $COCH_2$), 7.08 (dd, $^3J_{HH}$=3.9, 3.9 Hz, 1H, CH=C), 7.18–7.42 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.3 (OCH_2CH_3), 23.2, 25.9, 29.7 (CH_2), 52.1 (NCH_2Ph), 53.8 (CHNH), 60.3 (OCH_2CH_3), 126.7, 127.5, 128.1 (C_{arom}), 130.3 (C=CH), 140.3 (CH=C), 143.4 (C_{ipso}), 168.0 (C=O). IR (film, cm^{-1}): 3387 ν(NH), 1707 ν(C=O). MS (CI-isobutane): *m/z* 260 $[M+H]^+$. HRMS (CI) calc. for $C_{16}H_{21}O_2N+H$ $[M+H]^+$ 260.1650; found: 260.1659.

4.2.2. 6-Diethylamino-cyclohex-1-enecarboxylic acid ethyl ester (6). R_f (ethyl acetate/petroleum ether 1:1)=0.67. Yield: 66% (42.7 mg from 88.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.99 (t, $^3J_{HH}$=7.0 Hz, 6H, NCH_2CH_3), 1.29 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.40–1.85 (m, 4H, CH_2), 2.05–2.20 (m, 2H, CH_2), 2.50 (q, $^2J_{HH}$=7.0 Hz, 4H, $NHCH_2$), 3.75 (m, 1H, CHN), 4.20 (q, $^3J_{HH}$=7.1 Hz, 2H, $COCH_2$), 6.75 (ddd, $^3J_{HH}$=4.0, 4.0 Hz, $^4J_{HH}$=1.5 Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): δ=14.2 (OCH_2CH_3), 19.6, 21.0 (CH_2), 25.5 (NCH_2CH_3), 29.6 (CH_2), 44.0 (NCH_2CH_3), 53.4 (HCN), 65.8 (OCH_2CH_3), 121.9 (HC=C), 136.7 (HC=C), 167.4 (C=O). IR (film, cm^{-1}): 1715 ν(C=O). MS (EI, 70ev): *m/z* 225 $[M]^+$. HRMS (CI) calc. for $C_{13}H_{23}O_2N+H$ $[M+H]^+$ 226.1807; found: 226.1814.

4.2.3. (−)-(1*S*,6*S*)-6-(1-Phenyl-ethylamino)-cyclohex-1-ene-carboxylic acid ethyl ester (7a). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.64. Yield: 40% (40 mg from 112.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.33 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.39 (dd, $^3J_{HH}$=4.1, 7.0 Hz, 1.5H, CH_2), 1.53 (dd, $^3J_{HH}$=2.4, 13.3 Hz, 2H, CH_2), 1.62–1.70 (m, 2H, CH_2), 1.97–2.05 (10 lines, $^3J_{HH}$=3.8, 4.5 Hz, 1H, CH_2), 2.16–2.20 (two lines, 1H, CH_2), 3.66 (br s, 1H, CHNH), 3.93 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 4.17 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$), 4.19 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$), 6.99 (dd, $^3J_{HH}$=3.3, 3.8 Hz, 1H, CH=C), 7.16–7.36 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.3 (OCH_2CH_3), 24.1 ($CHCH_3$), 25.9, 27.4, 29.6 (CH_2), 49.8 (HNCH), 57.7 (HC–CH_3), 60.9 (OCH_2CH_3), 126.8, 126.9, 127.3, 128.2 (C_{arom}), 132.5 ($HCCH_2$=C), 142.4 (HC=C), 146.5 (C_{ipso}), 167.4 (C=O). IR (film, cm^{-1}): 3417 ν(NH), 1703 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1813. $[\alpha]_D^{20}=-105.3$ ($CHCl_3$, c=0.85) [from *S*-(−)PhCH(CH_3)-NH_2, $[\alpha]_D^{20}=-37.5$ (MeOH, c=3.0)].

4.2.4. (−)-(1*S*,6*R*)-6-(1-Phenyl-ethylamino)-cyclohex-1-enecarboxylic acid ethyl ester (7a′). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.48. Yield: 40% (39.8 mg from 112.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.39 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.79 (br s, 2H, CH_2), 1.91 (br s, 1H, CH_2), 2.08–2.13 (seven lines, $^3J_{HH}$=4.0, 5.5, 6.0 Hz, 2H, CH_2), 2.28 (dd, $^3J_{HH}$=9.6, 3.9 Hz, 1H, CH_2), 3.39 (br s, 1H, CHNH), 3.99 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 4.17 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 4.18 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 7.04 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CH=C), 7.34–7.38 (m, 5H, CH_{arom}) ^{13}C NMR ($CDCl_3$): δ=14.2 (OCH_2CH_3), 24.2 ($CHCH_3$), 25.8, 29.1, 30.3 (CH_2), 49.0 (HNCH), 55.1 ($HCCH_3$), 60.9 (OCH_2CH_3), 126.9, 127.9, 128.4, 128.8 (C_{arom}), 133.3 ($HCCH_2$=C), 145.9 (HC=C), 148.0 (C_{ipso}), 167.32 (C=O). IR (film, cm^{-1}): 3387 ν(NH), 1699 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1815. $[\alpha]_D^{20}=-13.9$ ($CHCl_3$, c=0.9) [from *S*-(−) PhCH(CH_3)NH_2, $[\alpha]_D^{20}=-37.5$ (MeOH, c=3.0)].

4.2.5. (+)-(1*R*,6*R*)-6-(1-Phenyl-ethylamino)-cyclohex-1-enecarboxylic acid ethyl ester (7b). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.64. Yield: 40% (28.6 mg from 81.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.32 (t, $^3J_{HH}$=7.2 Hz, 3H, OCH_2CH_3), 1.37 (d, $^3J_{HH}$=6.7 Hz, 3H, CH_3CH), 1.43–1.82 (m, 3H, CH_2), 2.05–2.27 (m, 3H, CH_2), 3.66 (br s, CHNH), 3.97 (q, $^3J_{HH}$=6.5 Hz, 1H, CH_3CH), 4.22 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$), 4.23 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$) 7.03 (dd, $^3J_{HH}$=3.4, 4.0 Hz, 1H, CH=C), 7.20–7.41 (m, 5H, CH_{arom}) ppm. $[\alpha]_D^{20}=+106.3$ ($CHCl_3$, c=0.45) [from *R*-(+) PhCH(CH_3)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **7a**.

4.2.6. (+)-(1*R*,6*S*)-6-(1-Phenyl-ethylamino)-cyclohex-1-enecarboxylic acid ethyl ester (7b′). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.48. Yield: 40% (28.2 mg from 81.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.27 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.38 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.76–2.25 (m, 6H, CH_2), 3.39 (br s, 1H, CHNH) 3.99 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 4.18 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 4.19 (q, $^3J_{HH}$=7.1 Hz, 1H OCH_2), 7.06 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CH=C), 7.24–7.37 (m, 5H, CH_{arom}) ppm. $[\alpha]_D^{20}=+20.6$ ($CHCl_3$, c=0.35) [from *R*-(+)PhCH(CH_3)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **7a′**.

4.2.7. (−)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8a). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.65. Yield: 38% (30.5 mg from 90.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.22 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.34 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.35–2.08 (m, 6H, CH_2, NH), 2.16–2.60 (m, 3H, CH_2), 3.82 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 3.91 (m, 1H, CHNH), 4.13 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 7.17 (m, 1H, CH=C), 7.19–7.50 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=16.0 (OCH_2CH_3), 23.7 ($CHCH_3$), 24.8, 27.6, 29.7, 30.4 (CH_2), 53.0, 56.6 (CHN or $CHCH_3$), 60.8 (OCH_2CH_3), 124.9 (C=CH), 125.9, 127.0, 128.5 (C_{arom}), 145.1 (C=CH), 146.7 (C_{ipso}), 168.1 (C=O). IR (film, cm^{-1}): 3460 ν(NH), 1703 ν(C=O). MS (CI, isobutane): *m/z* 288 $[M+H]^+$. HRMS (CI) calc. for $C_{18}H_{25}O_2N+H$ $[M+H]^+$ 288.1963; found: 288.1957. $[\alpha]_D^{20}=-36.5$ ($CHCl_3$, c=0.2) [from *S*-(−) PhCH(Me)NH_2, $[\alpha]_D^{20}=-37.5$ ($CHCl_3$, c=3.0)].

4.2.8. (+)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8a′). Single diastereoisomer: R_f

(ethyl acetate/petroleum ether 1:2)=0.45. Yield: 25% (20.0 mg from 90.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.24 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.38 (d, $^3J_{HH}$=6.5 Hz, 3H, CH_3CH), 1.46–2.10 (m, 6H, CH_2, NH), 2.15–2.68 (m, 3H, CH_2), 3.85 (q, $^3J_{HH}$=6.5 Hz, 1H, CH_3CH), 3.92 (m, 1H, CHNH), 4.12 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 7.12 (dd, $^3J_{HH}$=5.7, 5.7 Hz, 1H, CH=C), 7.23–7.37 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.2 (OCH_2CH_3), 23.5 (CH_3CH), 24.1, 26.0, 27.3, 28.1 (CH_2), 52.6, 55.6 (CHN or $CHCH_3$), 60.7 (OCH_2CH_3), 125.6 (C=CH), 126.6, 127.4, 128.3 (C_{arom}), 144.8 (C=CH), 146.5 (C_{ipso}), 168.0 (C=O). IR (film, cm^{-1}): 3400 ν(NH), 1704 ν(C=O). MS (CI, isobutane): *m/z* 288 $[M+H]^+$. HRMS (CI) calc. for $C_{18}H_{25}O_2N+H$ $[M+H]^+$ 288.1963; found: 288.1967; $[\alpha]_D^{20}=+4.9$ ($CHCl_3$, c=1.3) [from *S*-(−) PhCH(Me)NH_2, $[\alpha]_D^{20}=-37.5$ ($CHCl_3$, c=3.0)].

4.2.9. (+)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8b). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.65. Yield: 35% (18.7 mg from 60.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.23 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.41 (d, $^3J_{HH}$=6.5 Hz, 3H, CH_3CH), 1.58–1.85 (m, 6H, CH_2, NH), 2.25–2.49 (m, 3H, CH_2), 3.84 (m, 1H, CHNH), 3.92 (q, $^3J_{HH}$=6.3 Hz, 1H, CH_3CH), 4.12 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 4.14 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 7.16–7.37 (m, 6H, CH=C, CH_{arom}) ppm. $[\alpha]_D^{20}=+33.5$ ($CHCl_3$, c=0.2) [from *R*-(+) PhCH(Me)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **8a**.

4.2.10. (−)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8b′). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.45. Yield: 25% (13.0 mg from 60.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.25 (t, $^3J_{HH}$=7.2 Hz, 3H, OCH_2CH_3), 1.40 (d, $^3J_{HH}$=6.4 Hz, 3H, CH_3CH), 1.57–2.04 (m, 6H, CH_2, NH), 2.23–2.53 (m, 3H, CH_2), 3.85–3.90 (four lines, $^3J_{HH}$=2.1, 6.3 Hz, 2H, CH_3CH, CHNH), 4.12 (q, $^3J_{HH}$=7.2 Hz, 1H, OCH_2), 4.13 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 7.11–7.23 (m, 1H, CH=C), 7.28–7.35 (m, 5H, CH_{arom}) ppm. $[\alpha]_D^{20}=-6.8$ ($CHCl_3$, c=0.25) [from *R*-(+) PhCH(Me)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **8a′**.

4.2.11. 6-Azido-cyclohex-1-enecarboxylic acid ethyl ester (9). R_f (ethyl acetate/petroleum ether 1:1)=0.74. Yield: 65% (40.0 mg from 97.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.32 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.50–1.80 (m, 4H, CH_2), 1.90–2.42 (m, 2H, CH_2), 4.25 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 4.45 (m, 1H, CHN_3), 7.23 (dd, $^3J_{HH}$=2.4, 2.4 Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): δ=14.3 (OCH_2CH_3), 22.8, 24.1, 26.2 (CH_2), 55.2 (CHN_3), 60.9 (OCH_2CH_3), 131.8 (C=CH), 140.3 (HC=C), 167.8 (C=O). IR (film, cm^{-1}): 2100 ν(N_3), 1706 ν(C=O). MS (CI, isobutane): *m/z* 196 $[M+H]^+$. HRMS (CI) calc. for $C_9H_{13}O_2N_3+H$ $[M+H]^+$ 196.1086; found: 196.1081.

4.2.12. 6-Benzylamino-5-methyl-cyclohex-1-enecarboxylic acid ethyl ester (12). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.71. Yield: 31% (31.0 mg from 130.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.88 (d, $^3J_{HH}$=7.1 Hz, 3H, CH_3CH), 1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.38 (m, 1H, CH_2), 1.68 (bs, 1H, NH), 1.95 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 2.11–2.21 (m, 2H, CH_2, CH_3CH), 3.29 (d, $^3J_{HH}$=2.0 Hz, 1H, CHNH), 3.80 (AB, $^2J_{HH}$=12.7 Hz, 2H, CH_2NH), 4.19 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 7.06 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CH=C), 7.20–7.38 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.1 (OCH_2CH_3), 19.2 (CH_2), 22.3 (CH_3), 28.2 (CH_2), 35.1 ($CHCH_3$), 52.3 (NCH_2Ph), 54.4 (CHNH), 61.1 (OCH_2CH_3), 121.9 126.9, 127.2, 128.3 (C_{arom}), 130.2 (C=CH), 138.9 (HC=C), 141.2 (C_{ipso}), 165.5 (C=O). IR (film, cm^{-1}): 3420 ν(NH), 1708 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1814.

4.2.13. 6-Benzylamino-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (13). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.49. Yield: 49% (50.6 mg from 130.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.05 (d, $^3J_{HH}$=7.3 Hz, 3H, CH_3CH), 1.22 (m, 1H, CH_2), 1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.70 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 1.87 (bs, 1H, NH), 1.95 (m, 1H, CH_2), 2.40 (m, 1H, CH), 3.61 (dd, $^3J_{HH}$=5.1, 5.1 Hz, 1H, CHNH), 3.79 (AB, $^3J_{HH}$=7.1 Hz, 2H, $NHCH_2$), 4.19 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 6.92 (d, $^3J_{HH}$=5.0 Hz, 1H, CH=C), 7.20–7.36 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): 14.5 (OCH_2CH_3), 19.7 (CH_2), 20.5 (CH_3), 24.7 (CH_2), 30.0 ($CHCH_3$), 52.0 (NCH_2Ph), 55.4 (CHNH), 60.1 (OCH_2CH_3), 126.1 (C=CH), 126.9, 127.1, 128.0 (C_{arom}), 141.70 (C_{ipso}), 142.2 (HC=C), 165.5 (C=O). IR (film, cm^{-1}): 3400 ν(NH), 1705 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{24}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1810.

4.2.14. 6-Azido-5-methyl-cyclohex-1-enecarboxylic acid ethyl ester (14) and 6-Azido-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (15). Ratio of regioisomers: 2:1: R_f (ethyl acetate/petroleum ether 1:2)=0.73 and 0.66. Yield: 70% (41.0 mg from 95.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.97 (d, $^3J_{HH}$=7.7 Hz, 3H, CH_3CH, major), 1.05 (d, $^3J_{HH}$=7.3 Hz, 3H, CH_3CH, minor), 1.32 (t, $^3J_{HH}$=7.1 Hz, 6H, OCH_2CH_3), 1.34–1.50 (m, 2H, CH_2), 1.55–2.08 (m, 5H, CH_2), 2.15–2.35 (m, 2H, CH_2, CH), 2.41 (m, 1H, CH), 4.05 (d, $^3J_{HH}$=3.8 Hz, 1H, CHN_3, major), 4.25 (m, 4H, OCH_2), 4.38 (m, 1H, CHN_3, minor), 7.07 (d, $^3J_{HH}$=4.1 Hz, CH=C, 1H, minor), 7.19 (dd, $^3J_{HH}$=3.9, 3.9 Hz, 1H, CH=C, major) ppm. ^{13}C NMR ($CDCl_3$): δ=13.6, 14.1 (OCH_2CH_3), 14.8 (CH_3, major), 20.9, 22.4, 24.3, 25.1 (CH_2, major and minor), 30.6, 35.1 ($CHCH_3$, major and minor), 54.2 (CHN_3, minor), 57.8 (CHN_3, major), 61.7 (OCH_2CH_3, major), 63.1 (OCH_2CH_3, minor), 131.5 (C=CH, minor), 133.0 (C=CH, major), 140.3 (HC=C, major), 143.2 (HC=C, minor), 167.8 (C=O, major and minor). IR (film, cm^{-1}): 2112, 2110 ν(N_3), 1710 ν(C=O). MS (CI, isobutane): *m/z* 210 $[M+H]^+$. HRMS (CI) calc. for $C_{10}H_{15}O_2N_3+H$ $[M+H]^+$ 210.1242; found: 210.1247.

4.2.15. 6-Diethylamino-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (16). R_f (ethyl acetate/petroleum ether 1:2)=0.78. Yield: 78% (75.0 mg from 128.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.97 (t, $^3J_{HH}$=7.0 Hz, 6H, NCH_2CH_3), 0.99 (d, $^3J_{HH}$=7.1 Hz, 3H, CH_3CH), 1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.52 (m,

1H, CH_2), 1.67–1.95 (m, 2H, CH_2), 2.08–2.33 (m, 2H, CH, CH_2), 2.30–2.72 (m, 4H, NCH_2), 3.80 (m, 1H, CHN), 4.18 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.44 (d, $^3J_{HH}=2.7$ Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): $\delta=14.1$ (OCH_2CH_3), 20.0 (CH_2), 21.6 (CH_3), 27.2 (CH_2), 29.7 (NCH_2CH_3), 30.2 ($CHCH_3$), 45.8 (NCH_2CH_3), 56.1 (*C*HNH), 61.8 (OCH_2CH_3), 126.4 (*C*=CH), 135.5 (*C*H=C), 168.0 (C=O). IR (film, cm^{-1}): 1715 ν(C=O). MS (CI, isobutane): *m/z* 240 $[M+H]^+$. HRMS (CI) calc. for $C_{14}H_{25}O_2N+H$ $[M+H]^+$ 240.1963; found: 240.1959.

4.2.16. 6-Benzylamino-5-phenyl-cyclohex-1-enecarboxylic acid ethyl ester (17). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.65. Yield: 58% (70.0 mg from 140.0 mg of **1d**); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.32$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3), 1.82 (dd, $^3J_{HH}=6.7$, 12.8 Hz, 1H, CH_2), 2.04 (ddd, $^3J_{HH}=4.0$, 8.2, 13.5 Hz 1H, CH_2), 2.16 (ddd, $^3J_{HH}=4.1$, 8.6, 12.9 Hz 1H, CH_2), 2.23 (2×q, $^3J_{HH}=4.4$ Hz, 1H, CH_2), 2.30 (bs, 1H, NH), 3.19 (dt, $^3J_{HH}=4.1$, 7.3 Hz, 1H, PhCH) 3.79 (AB, $^2J_{HH}=12.6$ Hz, 2H, CH_2NH), 3.93 (d, $^3J_{HH}=4.0$ Hz, 1H, C*H*NH), 4.25 (q, $^3J_{HH}=7.0$ Hz, 2H, OCH_2), 7.15 (dd, $^3J_{HH}=3.8$, 3.8 Hz, 1H, CH=C), 7.19–7.32 (m, 10H, CH_{arom}) ppm. COSY (^{1}H–^{1}H): cross peak [$\delta=3.19$ (PhCH) and $\delta=3.93$ (C*H*NH), $\delta=7.15$ (CH=C) and $\delta=2.04$, 2.23 (CH_2)]. ^{13}C NMR ($CDCl_3$): 14.3 (OCH_2CH_3), 23.6, 25.7 (CH_2), 42.5 (*C*HPh), 51.8 (NCH_2Ph), 55.9 (*C*HNH), 60.5 (OCH_2CH_3), 126.2, 126.9, 127.5, 128.3, 128.3 (C_{arom}), 132.5 (*C*=CH), 140.4 (C_{ipso}), 142.7 (*C*H=C), 143.7 (C_{ipso}), 167.4 (C=O). IR (film, cm^{-1}): 3407 ν(N–H), 1715 ν(C=O). MS (CI, isobutane): *m/z* 336 $[M+H]^+$. HRMS (CI) calc. for $C_{22}H_{25}O_2N+H$ $[M+H]^+$ 336.1963; found: 336.1969.

4.2.17. 6-Diethylamino-3-phenyl-cyclohex-1-enecarboxylic acid ethyl ester (18). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.70. Yield: 60% (47.0 mg from 100.0 mg of **1d**); colorless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (t, $^3J_{HH}=7.1$ Hz, 6H, NCH_2CH_3), 1.27 (t, $^3J_{HH}=7.2$ Hz, 3H, OCH_2CH_3), 1.61–1.89 (m, 2H, CH_2), 1.92–2.31 (m, 2H, CH_2), 2.33–2.62 (m, 4H, NCH_2), 3.10 (m, 1H, PhCH), 4.02 (ddd, $^3J_{HH}=4.0$, 2.0, 2.0 Hz, 1H, C*H*N), 4.20 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.81 (d, $^3J_{HH}=1.8$ Hz, 1H, CH=C), 7.21–7.51 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): $\delta=14.1$ (OCH_2CH_3), 21.6, 29.7 (CH_2), 27.4 (NCH_2CH_3), 41.5 (*C*HPh), 45.8 (NCH_2CH_3), 52.4 (*C*HNH), 60.8 (OCH_2CH_3), 126.9, 127.5, 128.3 (C_{arom}), 132.8 (*C*=CH), 142.1 (C_{ipso}), 143.4 (*C*H=C), 168.0 (C=O). IR (film, cm^{-1}): 1711 ν(C=O). MS (CI, isobutane): *m/z* 302 $[M+H]^+$. HRMS (CI) calc. for $C_{19}H_{27}O_2N+H$ $[M+H]^+$ 302.2120; found: 302.2125.

4.2.18. 5-Phenyl-cyclohexa-1,5-dienecarboxylic acid ethyl ester (19).[14] R_f (ethyl acetate/petroleum ether 1:2)=0.90. Yield: 28% (23.0 mg from 140.0 mg of **1d**); colorless oil; ^{1}H NMR ($CDCl_3$): $\delta=1.33$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3), 2.35–2.80 (m, 4H, CH_2), 4.26 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.81 (dd, $^4J_{HH}=1.2$, 1.3 Hz, 1H, C=CHC) 7.01 (ddd, $^3J_{HH}=4.6$, 4.4 Hz, $^4J_{HH}=1.2$ Hz, 1H, CH_2CH=C), 7.15–7.65 (m, 5H, CH_{arom}) ppm. IR (film, cm^{-1}): 1710 ν(C=O). MS (CI, isobutane): *m/z* 229 $[M+H]^+$.

4.3. Hydrogenolysis

Amine **7a** (70 mg, 0.25 mmol), dissolved in MeOH (20 mL) was hydrogenated in the presence of Pd/C (50 mg) during 48 h at r.t. Then the catalyst was filtered off and solution was concentrated in vacuo to give the mixture (36 mg, 80%) of pure (1*R*, 2*S*)-*cis*[7b] and (1*S*, 2*S*)-*trans*[7c] 2-aminocyclohexanecarboxylic acid ethyl ester as colorless oil. The mixture was analyzed by GC (column hp1, 30 m, temperature gradient: 40 °C, 2 min; 10 °C/min, detector temperature 260 °C) retention time (min): minor isomer 8.21 (40.2%), major isomer 8.82 (59.8%), $[\alpha]_D^{20}=+35.6$ (EtOH, $c=0.5$), ^{1}H NMR ($CDCl_3$, 500 MHz, ^{1}H–^{1}H COSY): $\delta=1.27$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3, major and minor), 1.35–1.45 (m, 4H, CH_2, major and minor), 1.73 (br s, 2H, CH_2, major and minor), 1.80–1.87 (m, 2H, CH_2, major and minor), 2.20 (t, $^3J_{HH}=5.9$ Hz, 1H, CH, major), 2.33–2.38 (m, 3H, CH and NH, minor), 2.75 (t, $^3J_{HH}=5.9$ Hz, 1H, CH, major) 3.4 (t, $^3J_{HH}=6.2$ Hz, 1H, CH, minor), 3.77 (br s, 2H, NH major), 4.22 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2, major and minor). ^{13}C NMR ($CDCl_3$): $\delta=14.1$ (OCH_2CH_3, major and minor), 24.1 (CH_2, major), 24.5, 24.7 (CH_2, minor), 25.6 (CH_2, major), 25.8 (CH_2, minor), 28.5 (CH_2, major), 30.0 (CH_2, minor), 32.9 (CH_2, major), 47.1, 49.6 (CH, minor), 51.5, 52.4 (CH, major), 60.1 (OCH_2CH_3, minor), 61.3 (OCH_2CH_3, major), 173.9 (C=O, major). 174.1 (C=O, minor). MS (CI, isobutane): *m/z* 172 $[M+H]^+$, 100%; 158 $[M-N]^+$, 56%. Calculated the rotary power of the mixture of the 2-amino-cyclohexanecarboxylic acid ethyl ester: $[\alpha]_{D\,calcd}^{20}=(+56.3)$[7c] (0.598)+(−2.7)[7b] (0.402)=+32.6, a value in good agreement with the experimental value.[7d]

According to the described procedure the mixture of (1*S*, 2*R*)-*cis* and (1*R*, 2*R*)-*trans* 2-amino-cyclohexanecarboxylic acid ethyl ester[7a] from amine **7a′** was obtained as colorless oil. GC: retention time (min) minor isomer 8.41 (44.8%), major isomer 8.98 (55.2%), $[\alpha]_D^{20}=-27.9$ (EtOH, $c=0.75$), ^{1}H NMR ($CDCl_3$): $\delta=1.26$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3, major and minor), 1.34–1.78 (m, 4H, CH_2, major and minor), 1.97–2.34 (m, 5H, CH_2, CH, major and minor), 2.73–2.98 (m, 3H, NH minor, CH major), 3.02–3.36 (br s, 1H, CH, minor), 4.06–4.22 (m, 4H, NH, OCH_2, major and minor). $[\alpha]_{D\,calcd}^{20}=(-52.9)$[7a] (0.552)+(+0.9)[7a] (0.448)=−28.7. MS spectrum was identical to that of the mixture from amine **7a** obtained.

4.4. Synthesis of primary allylic amine 10

Triphenylphosphine and traces of water were added to a solution of azide **9** (0.31 mmol, 60 mg) in THF (5 mL) and resulted mixture was stirred at room temperature for 6 h. The precipitated triphenylphosphine oxide was filtered off and after evaporation of solvent the crude product was analyzed by ^{1}H NMR spectroscopy.

4.4.1. 6-Amino-cyclohex-1-enecarboxylic acid ethyl ester (10). Yield: 82% (42 mg); colorless oil; ^{1}H NMR ($CDCl_3$): $\delta=1.29$ (t, $^3J_{HH}=7.0$ Hz, 3H, OCH_2CH_3), 1.44–1.79 (m, 4H, CH_2), 2.04–2.37 (m, 4H, CH_2, NH_2), 3.92 (dd, $^3J_{HH}=6.8$ Hz, 1H, C*H*NH_2), 4.21 (q, $^3J_{HH}=7.0$ Hz, 2H, OCH_2), 7.32 (dd, $^3J_{HH}=2.8$, 2.8 Hz, 1H, CH=C). IR (film, cm^{-1}): 3414 ν(NH), 1698 ν(C=O). MS (CI, isobutane): *m/z* 170

$[M+H]^+$. HRMS (CI) calc. for $C_9H_{15}O_2N+H$ $[M+H]^+$ 170.1181; found: 170.1176.

4.5. Synthesis of allylic phosphonates 11, 20 and 21

To a solution of allylic phosphates **1a**, **1c** or **1d** (0.3 mmol) in dry toluene (5 mL), 0.6 mmol of trimethyl phosphite was added and the resulting mixture was stirred with heating up 60–90 °C under Ar. Progress of the reaction was followed by TLC chromatography. When the reaction was complete, solvent and volatile products were removed in vacuo and residue was purified by silica gel chromatography (*n*-hexane/EtOAc) to provide a pure allylic phosphonates **11**, **20** and **21** as a colorless oils.

4.5.1. 6-(Dimethoxy-phosphoryl)-cyclohex-1-enecarboxylic acid ethyl ester (11). R_f (ethyl acetate/petroleum ether 2:1)=0.50. Yield: 69% (77.0 mg from 130.0 mg of **1a**); colorless oil; ^{31}P NMR ($CDCl_3$): $\delta=31.5$ ppm. ^1H NMR ($CDCl_3$): $\delta=1.29$ (t, $^3J_{HH}=7.2$ Hz, 3H, OCH_2CH_3), 1.55–1.82 (m, 2H, CH_2CHP), 1.91–2.15 (m, 1H, CH_2), 2.19–2.31 (m, 3H, CH_2), 3.28 (ddd, $^2J_{HP}=24.0$ Hz, $^3J_{HH}=1.3$, 5.3 Hz, 1H, CHP), 3.68 (d, $^3J_{HP}=10.8$ Hz, 3H, OCH_3), 3.74 (d, $^3J_{HP}=10.7$ Hz, 3H, OCH_3), 4.19 (2×q, $^3J_{HH}=7.2$ Hz, 2H, OCH_2), 7.03 (dd, $^3J_{HH}=4.4$, 8.4 Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): $\delta=14.2$ (s, OCH_2CH_3), 17.9 (d, $^4J_{CP}=1.3$ Hz, CH_2), 22.5 (d, $^3J_{CP}=4.4$ Hz, CH_2), 24.9 (d, $^2J_{CP}=2.9$ Hz, CH_2), 31.3 (d, $^1J_{CP}=137.9$ Hz, CHP), 52.5 (d, $^2J_{CP}=7.3$ Hz, OCH_3), 52.6 (d, $^2J_{CP}=7.3$ Hz, OCH_3), 60.6 (s, OCH_2), 126.5 (d, $^2J_{CP}=8.5$ Hz, CH=*C*), 141.9 (d, $^3J_{CP}=10.4$ Hz, *C*H=C), 166.8 (s, C=O) ppm. IR (film, cm^{-1}): 1712 ν(C=O), 1645 ν(C=C), 1249 ν(P=O). MS (CI, isobutane): *m/z* 263 $[M+H]^+$. HRMS (CI) calc. for $C_{11}H_{19}O_5P+H$ $[M+H]^+$ 263.1048; found: 263.1054.

4.5.2. 6-(Dimethoxy-phosphoryl)-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (20). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 2:1)=0.44. Yield: 70% (63.0 mg from 107.0 mg of **1c**); colorless oil; ^{31}P NMR ($CDCl_3$): δ 32.7 ppm. ^1H NMR ($CDCl_3$, 500 MHz): $\delta=1.02$ (d, $^3J_{HH}=7.4$ Hz, 3H, CH_3CH), 1.28 (t, $^3J_{HH}=7.0$ Hz, 3H, OCH_2CH_3), 1.70–1.81 (m, 2H, CH_2CHP), 2.02–2.21 (m, 2H, CH_2CHCH_3), 2.44 (m, 1H, CH_3CH), 3.31 (ddd, $^2J_{HP}=25.0$ Hz, $^3J_{HH}=5.2$, 1.5 Hz, 1H, CHP), 3.66 (d, $^3J_{HP}=10.8$ Hz, 6H, OCH_3), 4.20 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.89 (t, $^3J_{HH}=^4J_{HP}=4.2$ Hz, 1H, CH=C) ppm. COSY (^1H–^1H): cross peak [$\delta=2.44$ ($CHCH_3$) and $\delta=1.02$ (CH_3CH) and $\delta=6.89$ (CH=C)]. ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=14.1$ (s, OCH_2CH_3), 19.1 (d, $^3J_{CP}=3.9$ Hz, CH_2CHCH_3), 20.7 (s, CH_3CH), 25.6 (s, CH_2CHP), 28.7 (s, CH_3CH), 31.5 (d, $^1J_{CP}=138.4$ Hz, CHP), 52.7 (d, $^2J_{CP}=7.4$ Hz, OCH_3), 53.0 (d, $^2J_{CP}=7.4$ Hz, OCH_3), 60.7 (s, OCH_2), 125, 5 (d, $^2J_{CP}=8.6$ Hz, CH=*C*), 147.0 (d, $^3J_{CP}=10.4$ Hz, *C*H=C), 174.7 (s, C=O) ppm. IR (film, cm^{-1}): 1712 ν(C=O), 1250 ν(P=O). MS (CI, isobutane): *m/z* 277 $[M+H]^+$. HRMS (CI) calc. for $C_{12}H_{21}O_5P+H$ $[M+H]^+$ 277.1205; found: 277.1212.

4.5.3. 6-(Dimethoxy-phosphoryl)-5-phenyl-cyclohex-1-enecarboxylic acid ethyl ester (21). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 2:1)=0.47. Yield: 90% (119.0 mg from 150.0 mg of **1d**); colorless oil; ^{31}P NMR ($CDCl_3$): δ 30.9 ppm. ^1H NMR ($CDCl_3$, 500 MHz): $\delta=1.42$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3), 1.90–2.13 (m, 2H, CH_2), 2.35 (m, 1H, CH_2), 2.50 (m, 1H, CH_2), 3.70–3.75 (m, 1H, seven lines, $^3J_{HP}=12.5$ Hz, PhCH), 3.82 (d, $^3J_{HP}=10.8$ Hz, 3H, $POCH_3$), 3.85 (d, $^3J_{HP}=10.8$ Hz, 3H, $POCH_3$), 3.86 (dd, $^2J_{HP}=23.0$ Hz, $^3J_{HH}<1$ Hz, 1H, CHP), 4.37 (m, 2H, OCH_2), 7.15 (dd, $^4J_{HP}=4.0$ Hz, $^3J_{HH}=3.8$ Hz, 1H, CH=C), 7.20–7.38 (m, 5H, CH_{arom}) ppm. ^1H {^{31}P} NMR: $\delta=3.73$ (six lines, CHPh), 3.82 (s, $POCH_3$), 3.85 (s, $POCH_3$), 3.86 (s, $^3J_{HH}<1$ Hz, 1H, CHP), 7.15 (d, $^3J_{HH}=3.8$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=14.2$ (s, OCH_2CH_3), 21.7 (d, $^3J_{CP}=2.7$ Hz, CH_2CHPh), 25.4 (s, CH_2CH=C), 35.6 (d, $^1J_{CP}=138.2$ Hz, CHP), 36.4 (s, CHPh), 52.8 (d, $^2J_{CP}=6.8$ Hz, $POCH_3$), 52.9 (d, $^2J_{CP}=6.8$ Hz, $POCH_3$), 60.8 (s, $COCH_2$), 125.8 (d, $^3J_{CP}=9.3$ Hz, CH=*C*), 125.9, 126.7, 128.5 (s, CH_{arom}), 142.1 (d, $^3J_{CP}=10.6$ Hz, *C*H=C), 143.4 (d, $^3J_{CP}=16.5$ Hz, C_{ipso}), 166.9 (s, C=O) ppm. IR (film, cm^{-1}): 1712 ν(C=O), 1234 ν(P=O). MS (CI, isobutane): *m/z* 339 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_5P+H$ $[M+H]^+$ 339.1361; found: 339.1355.

Acknowledgements

This work was supported by the State Committee for Scientific Research, Poland (No 7T09A 148 21).

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