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Tetrahedron: *Asymmetry* 15 (2004) 445–452
Tetrahedron: *Asymmetry*

The use of nonactivated iminodienophiles in the stereoselective aza-Diels–Alder reaction

Anna Trifonova and Pher G. Andersson*

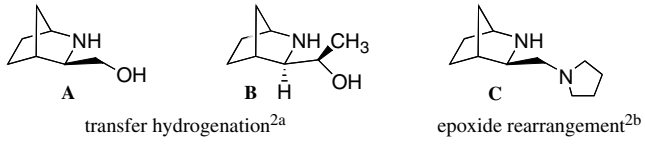
Department of Organic Chemistry, Institute of Chemistry, Uppsala University, Box 599, SE-75124 Uppsala, Sweden

Received 19 October 2003; accepted 3 December 2003

Abstract—This paper describes the preparation of nitrogen-containing bicycles by the aza-Diels–Alder reaction of nonactivated iminodienophiles and cyclopentadiene. Readily available starting materials such as (*S*)-(−)-lactate and L-amino acids were used for the preparation of chiral aldehydes with high enantiomeric excess. The improved oxidation procedure by Dess–Martin periodinane was employed for the synthesis of L-alanine derived phthalimide protected aldehyde **14**, which was difficult to obtain in high enantiomeric excess by other methods. The influence of different Lewis acids on the stereoselectivity of the aza-Diels–Alder reaction was also investigated: It was found that the use of a combination of $BF_3{\cdot}Et_2O$ and TFA in the cycloaddition leads to complete racemization of the imine prepared from **14** whereas the use of $TiCl_4$ gives the cycloaddition products **17a** and **17b** with high enantioselectivity (90%).

1. Introduction

The stereoselective aza-Diels–Alder reaction is a well-known method for the preparation of nitrogen-containing monocyclic- and bicyclic molecules.[1] The latter compounds have been widely used as chiral ligands in asymmetric synthesis.[2,3] For example, compounds **A** and **B** have been used for transfer hydrogenation[2a] of prochiral ketones (Scheme 1). Compound **C** has been used by Södergren et al.[2b] in the lithium amide base promoted chiral rearrangement of epoxides (Scheme 1). Therefore an efficient synthesis of these bicyclic amines as well as related compounds should find broad application. The reaction employed previously for the synthesis of nitrogen-containing bicycles was described by the groups of Stella and co-workers,[4a,b] Waldmann et al.[4c] and Bailey et al.,[4d,e] and it involves the condensation of cyclic dienes and an electron-deficient glyoxylate imine followed by transformation of the ester group into the desired functionality.[2] A new route based on the use of nonactivated imine dienophiles would broaden the scope of the synthesis considerably.



Scheme 1. Some examples of the ligands used in asymmetric transformations.

2. Results and discussion

There are few examples in the literature describing the use of nonactivated imines in the aza-Diels–Alder reaction.[5] Due to the low reactivity (or poor electrophilicity) of the imine functionality, [4+2] cycloaddition is possible only with highly reactive dienes under Lewis acid catalysis.[6–9] In order to investigate the scope of the reaction, a variety of optically active aldehydes was synthesized and evaluated. Aldehyde **1**[10] was prepared from commercially available methyl (*S*)-(−)-lactate in three steps[11]. Imine formation reaction with benzylamine in CH_2Cl_2 at 0 °C in the presence of $MgSO_4$ as a drying agent[7b] yielded the iminodienophile **2**, which was used in the cycloaddition without further purification (Scheme 2). The enantiomeric excess of aldehyde **1** was confirmed by treatment with (*S*)-1-phenylethyl amine and subsequent ^{13}C NMR analysis of the resulting chiral imine. It was found that no significant racemization occurred during oxidation and imine formation steps.

* Corresponding author. Tel.: +46-184713801; fax: +46-185120524; e-mail: phera@kemi.uu.se

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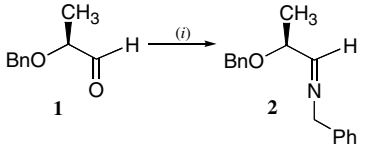
doi:10.1016/j.tetasy.2003.12.011

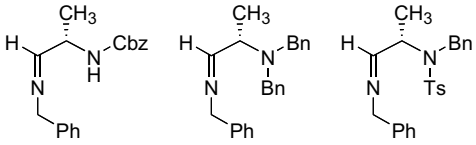


Scheme 2. Synthesis of imine **2**. Reagents and conditions: (i) $BnNH_2$, $MgSO_4$, CH_2Cl_2, 0 °C.

The Diels–Alder reaction of **2** with cyclopentadiene was catalyzed by $BF_3{\cdot}Et_2O$/TFA and gave rise to four diastereomers **3a**, **3b**, **3c**, and **3d** (Table 1), which were readily separated by silica gel chromatography or HPLC methods (see Experimental part). The relative configuration of the major bicyclic product **3a** was found to be *exo* by a NOESY NMR experiment, while the absolute configuration was tentatively assigned as shown in Table 1. The enantiomeric purity of compound **3a** was determined by chiral HPLC (see Experimental part). It was found that no racemization had occurred in the last three steps (Swern oxidation, imine formation, and Diels–Alder reaction).

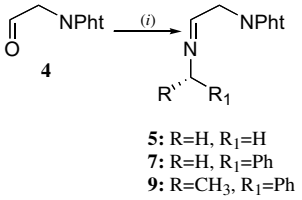
The aza-Diels–Alder reaction of the imine **2** with 1,3-cyclohexadiene and isoprene was also examined. Because of the low reactivity of these dienes, different Lewis acids were evaluated for the activation of the imine. Addition of $BF_3{\cdot}Et_2O$/TFA, $LiClO_4$, $ZnCl_2$, MgI_2, $MgI_2{\cdot}Et_2O$, Et_3Al, $Nd(OTf)_3$ did not improve the yield of the cyclic product and the unreacted imine remained in the reaction mixture even after 7–10 days. When the reactions were carried out at an elevated temperature, total decomposition of the starting material took place. The use of more potent Lewis acids such as $TiCl_4$ or $SnCl_4$ as well as carrying out the reaction in an ultrasonic bath gave a polymeric material of unidentified structure. The procedure involving the formation of iminium cation in aqueous solution in the presence of lanthanide triflate failed as well. The best result was obtained when isoprene was reacted with the imine activated by an excess (2.5 equiv) of freshly prepared $ZnCl_2{\cdot}Et_2O$, but the yield was low (~20%). 1,3-Cyclohexadiene was found to be less reactive than isoprene and the best yield obtained was <10%.

Since bicycles containing a pendant nitrogen could be potentially useful as ligands in asymmetric synthesis, we also investigated the preparation of such compounds by the aza-Diels–Alder reaction of a nonactivated imine with cyclopentadiene. The choice of the protecting group for the aminoaldehyde precursor was found to be crucial. Preliminary experiments showed that the iminodienophiles prepared from aminoaldehydes having protecting groups such as benzyl, benzyloxycarbonyl, and tosyl (Scheme 3) did not undergo the cycloaddition reaction. The reason for this observation could be the steric hindrance caused by the protecting groups. It was later found that the iminodienophiles prepared from less bulky phthalimide and succinimide aldehyde derivatives smoothly underwent aza-Diels–Alder reaction with cyclopentadiene to give cycloadducts in excellent yields.



Scheme 3. Amino imines tried in the aza-Diels–Alder reaction.

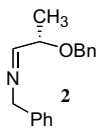
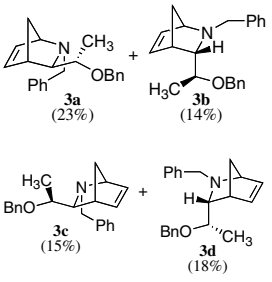
Phthalimide protected aldehyde **4**[13] (Scheme 4) was prepared in two steps.[14] This aldehyde was then reacted with three different amines: ethylamine, benzylamine, and (*S*)-1-phenylethylamine to give the corresponding imines **5**, **7**, and **9**, which were used directly in the next step. The $BF_3{\cdot}Et_2O$/TFA catalyzed cycloaddition between the imine and cyclopentadiene resulted in for-



5: R=H, R_1=H
7: R=H, R_1=Ph
9: R=CH_3, R_1=Ph

Scheme 4. Synthesis of imines **5**, **7** and **9**. Reagents and conditions: (i) appropriate amine, 4 Å molecular sieves, CH_2Cl_2.

Table 1. The products and the yields of aza-Diels–Alder reaction of imine **2** (the absolute stereochemistry of the products is tentatively assigned)

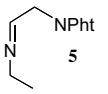
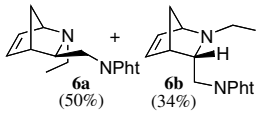
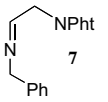
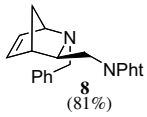
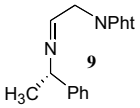
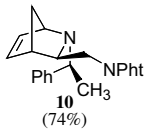
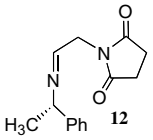
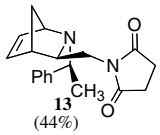
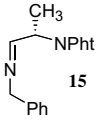
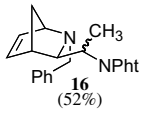
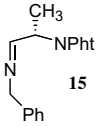
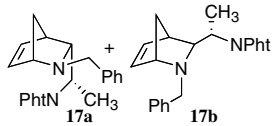
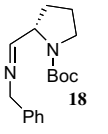
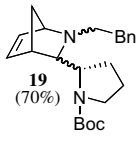
Entry	Imine	Lewis acid	Yield (%)[a]	*exo*/*endo* Selectivity	Diastereoselectivity[b]	Major products (isol. yield)
1		$BF_3{\cdot}Et_2O$/TFA	70	55:45[c]	60:40[c]	

[a] Total yield of diastereomers.
[b] Diastereoselectivity of the *exo* product.
[c] Determined after separation of the products.

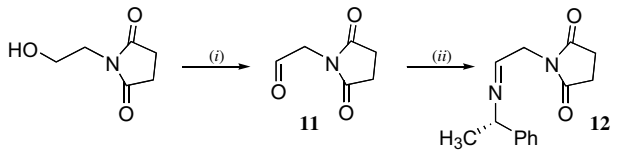
mation of bicycles **6a**, **6b**, **8**, and **10** (Table 2). Compounds **6a** and **8** were isolated as racemic mixtures with relative *exo* configuration because of the absence of a chiral moiety in the starting material. The relative configuration of racemic compound **6b** was determined as *endo*. In the case of product **10** with *exo* relative configuration it was not possible to detect the formation of the other *exo* diastereomer by ^{1}H NMR. The succinimide derivative **11** (Scheme 5) was obtained in two steps by reaction of 2-aminoethanol with succinic anhydride,[15] followed by Dess–Martin oxidation.[16b,c] Compound **11** was treated with (*S*)-1-phenylethylamine and the resulting imine **12** was subjected to the aza-Diels–Alder reaction with cyclopentadiene catalyzed by $BF_3{\cdot}Et_2O$/TFA to produce compound **13** with *exo* configuration in good yield.

The preparation of the aminobicycles having an additional stereogenic center was accomplished by employing aminoaldehydes prepared from available D- and

Table 2. The products and the yields of the aza-Diels–Alder reaction of imines **5**, **7**, **9**, **12**, **15**, and **18** (the absolute stereochemistry of the products is tentatively assigned)

Entry	Imine	Lewis acid	Yield (%)[a]	*exo*/*endo* Selectivity	Diastereoselectivity[b]	Major products (isol. yield of pure isomers)
1	 **5**	$BF_3{\cdot}Et_2O$/TFA	84	60:40[e]	n.a.	 **6a** (50%) **6b** (34%)
2	 **7**	$BF_3{\cdot}Et_2O$/TFA	95	85:15[d]	n.a	 **8** (81%)
3	 **9**	$BF_3{\cdot}Et_2O$/TFA	87	85:15[d]	99:1[d]	 **10** (74%)
4	 **12**	$BF_3{\cdot}Et_2O$/TFA	62	80:20[f]	88:12[f]	 **13** (44%)
5[g,h]	 **15**	$BF_3{\cdot}Et_2O$/TFA	89	72:28[c]	72:28[c]	 **16** (52%)
6[g]	 **15**	$TiCl_4$	40	45:55[f]	99:1[f]	 **17a** (22%) **17b** (18%)
7[h]	 **18**	$BF_3{\cdot}Et_2O$/TFA	70	n.d.	55:45[e]	 **19** (70%)

[a] Total yield of diastereomers.
[b] Diastereoselectivity of the *exo* product.
[c] Determined after separation of the products.
[d] Determined by HPLC analysis of the crude mixture.
[e] Determined by ^{13}C NMR experiment of the crude mixture.
[f] Determined by ^{1}H NMR experiment of the crude mixture.
[g] When the combination of $BF_3{\cdot}Et_2O$/TFA was used as a catalyst, the ee of the major product 0–80%, when $TiCl_4$ was used as a catalyst, the ee of the major product 90%.
[h] The pure isomers were not separated, the yield in brackets is given for the mixture of compounds.



Scheme 5. Synthesis of imine 12. Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, rt; (ii) $BnNH_2$, 4 Å molecular sieves, CH_2Cl_2.

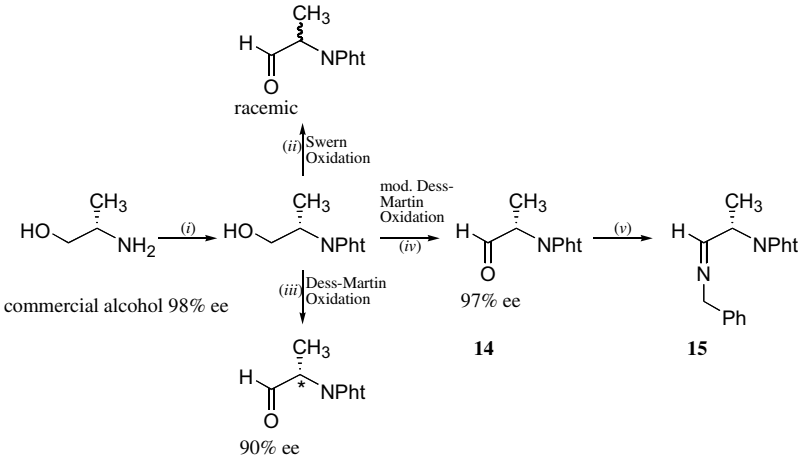
L-amino acids. To avoid racemization at the α-carbon during the preparation of the phthalimide aldehyde derivative, a convenient two-step procedure was employed (Scheme 6). First, the amino group of L-alaninol was protected[16a] to give the corresponding phthalimide. In the next step the choice of the oxidation procedure was found to be crucial due to ready racemization at the α-carbon. The preparation of aminoaldehyde **14** was reported earlier[16d–f] but the product was obtained in partially racemic form. The use of Swern oxidation resulted in the complete loss of optical activity of the product while Dess–Martin oxidation at standard conditions[16b,c] gave a partially racemic compound (Scheme 6). However, when the oxidation by Dess–Martin periodinane was performed in the presence of an excess of $NaHCO_3$ it was possible to obtain the aldehyde **14** with an enantiomeric excess of 97%. In this case it was important to keep the pH of the reaction above 5 and carry out complete neutralization of the acid released in the aqueous workup. The product of this modified Dess–Martin oxidation was treated with (*S*)-1-phenylethylamine in CH_2Cl_2 in presence of $MgSO_4$ at 0 °C[16g] to give the corresponding imine **15**. Its ^{13}C NMR spectrum was compared with the spectrum of the mixture of diastereomeric imines produced from racemic aldehyde. This experiment[16i] showed that no significant racemization had taken place during the oxidation and imine preparation steps. When the enantiomerically pure imine **15** was used in the aza-Diels–Alder reaction under standard conditions compound **16** was formed as the major product. Its relative configuration was determined to be *exo* by a NOESY NMR experiment. However, when the product was analyzed by chiral HPLC it was found that total or partial racemization had taken place during the cycloaddition reaction probably due to the acidic conditions ($TFA/BF_3{\cdot}Et_2O$). Because the presence of labile hydrogen at the α-carbon to amino group the protonation of imine nitrogen by TFA results in imine–enamine equilibrium with concomitant racemization of the α-carbon. When the trifluoroacetic acid and $BF_3{\cdot}Et_2O$ were excluded from the reaction mixture and $TiCl_4$ was used as a catalyst, better results were obtained. Surprisingly, in this case the configuration of the major product of the cycloaddition **17a** was determined as *endo*. This product was formed with high enantioselectivity (90%) but in lower yield (40%) (Table 2).

When the commercially available aldehyde **18** was used in the aza-Diels–Alder reaction, a relatively high yield of a mixture of diastereomers **19** was obtained (70%). However, it was not possible to separate the products or to determine the level of diastereoselectivity in this reaction because of the complete overlap of the signals in the NMR spectra and very similar retention times of the products in HPLC analysis.

The extension of the present aza-Diels–Alder reaction to other nonactivated aldehydes (for example, aldehydes having protected thiol function) and further applications of these compounds in asymmetric transformations are under investigation.

3. Experimental section

^1H, ^{13}C, and NOESY NMR spectra were recorded in $CDCl_3$ solutions at 399.95/100.57 MHz. The chemical shifts of protons are reported using the residual signal of ^1H in $CDCl_3$ as the internal reference (δ 7.26 ppm) and chemical shifts of carbons are reported setting a reference 76.9 ppm at the middle line of ^{13}C signal of $CDCl_3$. Optical rotations were recorded on a thermostated



Scheme 6. Synthesis of imine **15**. Reagents and conditions: (i) phthalic anhydride, triethylamine, toluene, 130 °C; (ii) oxalyl chloride, DMSO, triethylamine, CH_2Cl_2, −78 °C; (iii) Dess–Martin periodinane, CH_2Cl_2, rt; (iv) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (v) $BnNH_2$, $MgSO_4$, CH_2Cl_2, 0 °C.

polarimeter using a 1.0 dm cell. HPLC analyses were carried out using a chiral column (ChiralCel OD-H or OJ), a 254 nm UV detector and isopropanol/hexane (1:99) as eluent with flow rate 0.5 ml/min. Flash chromatography was performed on silica gel (37–70 μm) and Al_2O_3 gel (0.063–0.2 mm). The TLCs were performed on precoated plates, silica gel 60 F_{254}. The chiral starting materials, amines, acids, and other reagents were used as received from commercial suppliers. Dichloromethane was dried over CaH_2 and distilled under nitrogen. Cyclopentadiene was distilled prior to use.

3.1. 2-Succinimidoethanal 11

N-(2-Hydroxyethyl) succinimide[13] (0.30 g, 2.1 mmol) was dissolved in CH_2Cl_2 (21 ml, 10 ml/mmol) under a nitrogen atmosphere and Dess–Martin periodinane (1.42 g, 3.35 mmol) was added to the solution. After the completion of the reaction (by TLC) the reaction mixture was diluted with diethyl ether and solid K_2CO_3 was added. Since the resulting aminoaldehyde **11** is water soluble, the aqueous workup was avoided. The solids were filtered off and washed with CH_2Cl_2 and the solvents were evaporated giving crude aldehyde **11**. The traces of acetic acid were removed by coevaporation with toluene (three times). The crude material was subjected to column chromatography on silica gel using MeOH/CH_2Cl_2 (0–1.5% MeOH) as eluent to yield compound **11** (0.29 g, 2.05 mmol, 98%) as colorless oil. $R_f = 0.41$ (CH_2Cl_2/MeOH 9:1); IR (neat) ν 1712, 1418, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.54 (s, 1H), 4.38 (s, 2H), 2.81 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 192.3, 176.1, 47.9, 28.15 ppm; HRMS (FAB$^+$) (M+H$^+$): calcd for $C_6H_8NO_3$ 142.0504, found 142.0502.

3.2. (2*S*)-2-Phthalimidopropanal 14

Phthalimide protected (*S*)-alaninol[16a] (0.64 g, 3.1 mmol) was dissolved in CH_2Cl_2 (30 ml, 10 ml/mmol) under a nitrogen atmosphere and solid $NaHCO_3$ (5.16 g, 61.4 mmol) was added to the solution. The Dess–Martin periodinane (2.08 g, 4.9 mmol) was added to the mixture and it was intensively stirred for 0.5 h. The pH of the reaction mixture was kept ~6 during the oxidation by addition of solid $NaHCO_3$. After the completion of the reaction (by TLC) the reaction mixture was diluted with diethyl ether and after 15 min poured into a saturated solution of $NaHCO_3/Na_2S_2O_3$. The stirring was continued until there was complete neutralization of the released acid. The water phase was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, and evaporated yielding compound **14** (0.62 g, 3.0 mmol, 97%) as white crystals (recrystallized from CH_2Cl_2/hexane). $R_f = 0.19$ (ethyl acetate/pentane 2:8); mp 109 °C;[16d] $[\alpha]_D^{22} = -43$ (*c* 1.0, C_6H_6);[16g] IR (neat) ν 1960, 1816, 1721, 1479, 1388, 1036 cm^{-1};[16h] ^1H NMR ($CDCl_3$) δ 9.67 (s, 1H), 7.87–7.85 (m, 2H); 7.84–7.73 (m, 2H), 4.73 (q, $J = 7.1$ Hz, 1H), 1.59 (d, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 196.7, 168.7, 134.2, 123.4, 53.8, 12.7 ppm; HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{11}H_{10}NO_3$ 204.0661, found 204.0673.

3.3. The general procedure for imine preparation and the aza-Diels–Alder reactions with aldehydes 1 and 14

The aldehyde (1 equiv) was dissolved in 20 ml of CH_2Cl_2 under a nitrogen atmosphere and $MgSO_4$ (0.5 g/mmol) was added. The reaction mixture was cooled down to 0 °C using an ice bath and benzylamine [or (*S*)-1-phenylethylamine for investigation of enantiomeric purity of the aldehydes] (1 equiv) was added. After the imine formation was complete (~2 h by ^1H and ^{13}C NMR) the $MgSO_4$ was filtered off and the solvent was evaporated. The crude imine was redissolved in CH_2Cl_2 and cooled down in an acetone/dry ice bath to −78 °C followed by the addition of $BF_3{\cdot}Et_2O$ (1 equiv) and trifluoroacetic acid (1 equiv). The freshly distilled cyclopentadiene (2 equiv) was added dropwise and the reaction mixture was allowed to warm up to room temperature overnight. The work up using saturated aqueous $NaHCO_3$ was followed by extraction with CH_2Cl_2, drying the organic phase over $MgSO_4$ and evaporation of the solvent yielding the oily crude material, which was purified on a silica gel column using MeOH/CH_2Cl_2 (0–2.5% MeOH) as an eluent, and additionally purified from polymeric byproducts on Al_2O_3 gel column using CH_2Cl_2 as an eluent.

3.4. The general procedure for imine preparation and the aza-Diels–Alder reactions with aldehydes 5, 11, and 18

To 4 Å molecular sieves (0.2 g/mmol) in CH_2Cl_2 (2 ml/mmol) the aldehyde (1 equiv) was added under nitrogen and with stirring. After that benzylamine [or (*S*)-1-phenylethylamine or 2.0 M ethylamine solution in dry THF] (1 equiv) was added. The reaction mixture was stirred at room temperature until the imine formation was complete (usually 2–3 h according to ^1H NMR). The reaction mixture was cooled down to −78 °C using an acetone/dry ice bath followed by addition of $BF_3{\cdot}Et_2O$ (1 equiv) and trifluoroacetic acid (1 equiv). The freshly distilled cyclopentadiene (2 equiv) was added dropwise and the reaction mixture was allowed to warm up to room temperature overnight. Workup and purification were performed as described for compounds **1** and **14**.

3.5. (3*R*)-2-Benzyl-3-((1*S*)-benzyloxyethyl)-2-azabicyclo-[2.2.1]-hept-5-ene 3a

Separated by HPLC using isopropanol/hexane (2:98) as an eluent. Yield: 0.94 g (2.94 mmol, 23%) (colorless oil). $R_f = 0.54$ (MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{24} = -42.5$ (*c* 1.06, $CHCl_3$); IR (neat) ν 2981, 1453, 1220, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.23 (m, 10H), 6.49–6.47 (m, 1H), 6.11 (dd, $J = 5.7$, 1.6 Hz, 1H), 4.72 (s, 2H), 3.90 (d, $J = 12.8$ Hz, 1H), 3.66 (m, 1H), 3.52–3.48 (m, 1H), 3.20 (d, $J = 12.8$ Hz, 1H), 2.73 (d, $J = 1.3$ Hz, 1H), 1.79 (d, $J = 7.7$ Hz, 1H), 1.71 (d, $J = 8.1$ Hz, 1H), 1.28–1.23 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) 140.2, 139.2, 137.45, 132.1, 128.8, 128.1, 128.0, 127.5, 127.1, 126.5, 79.6, 71.7, 68.6, 62.3, 59.0, 45.5, 45.3, 17.6 ppm; HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{22}H_{26}NO$ 320.2014, found 320.2012.

3.6. (3*S*)-2-Benzyl-3-((1*S*)-benzyloxyethyl)-2-azabicyclo-[2.2.1]-hept-5-ene 3b

Yield: 0.56 g (1.75 mmol, 14%) (yellow oil). $R_f = 0.43$ (MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{24} = -27$ (*c* 1.0, $CHCl_3$); IR (neat) *v* 3062, 3027, 2970, 2929, 2867, 1495, 1453, 1372, 1333, 1166, 1091, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49–7.26 (m, 10H), 6.40–6.38 (m, 1H), 6.16–6.14 (m, 1H), 4.70 (s, 2H), 4.43 (d, $J = 13.9$ Hz, 1H), 3.62 (d, $J = 13.9$ Hz, 1H), 3.57 (m, 1H), 3.28–3.23 (m, 1H), 3.06 (d, $J = 1.1$ Hz), 2.73 (dd, $J = 9.0$, 2.7 Hz, 1H), 1.85 (d, $J = 8.2$ Hz, 1H), 1.54 (d, $J = 8.2$ Hz, 1H), 1.25 (d, $J = 6.2$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 143.8, 141.9, 140.7, 136.4, 131.0, 130.8, 130.7, 130.6, 130.1, 129.7, 129.0, 83.3, 74.2, 72.4, 66.3, 63.8, 48.8, 46.9, 20.3 ppm; HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{22}H_{26}NO$ 320.2014, found 320.2015.

3.7. (3*R*)-2-Benzyl-3-((1*S*)-benzyloxyethyl)-2-azabicyclo-[2.2.1]-hept-5-ene 3c

Yield: 0.62 g (1.94 mmol, 15%) (yellow oil). $R_f = 0.77$ (MeOH/CH_2 Cl_2 1:9); $[\alpha]_D^{24} = +76$ (*c* 1.15, $CHCl_3$); IR (neat) *v* 2982, 2868, 1495, 1453, 1368, 1107, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.29 (m, 10H), 6.56–6.54 (m, 1H), 6.20 (dd, $J = 5.5$, 1.5 Hz, 1H), 4.75 (d, $J = 11.6$ Hz, 1H), 4.57 (d, $J = 11.6$ Hz, 1H), 3.74 (d, $J = 13.3$ Hz, 1H), 3.65 (m, 1H), 3.52–3.45 (m, 1H), 3.28 (d, $J = 13.3$ Hz, 1H), 1.76–1.74 (m, 2H), 1.47 (d, $J = 6.2$ Hz, 3H), 1.30 (d, $J = 8.2$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 139.8, 138.7, 137.4, 132.5, 128.5, 128.1, 128.0, 127.6, 79.1, 70.7, 68.2, 62.2, 58.6, 45.4, 45.1, 17.9 ppm; HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{22}H_{26}NO$ 320.2014, found 320.2018.

3.8. (3*S*)-2-Benzyl-3-((1*S*)-benzyloxyethyl)-2-azabicyclo-[2.2.1]-hept-5-ene 3d

Separated by HPLC using isopropanol/hexane (2:98) as an eluent. Yield: 0.71 g (2.22 mmol, 18%) (light-yellow oil). $R_f = 0.52$ (MeOH/CH_2Cl_2 1:9); $[\alpha]_D^{24} = +135$ (*c* 0.80, $CHCl_3$); IR (neat) *v* 2870, 1452, 1219, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.24 (m, 10H), 6.20–6.18 (m, 1H), 5.91–5.89 (m, 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 4.37 (d, $J = 11.6$ Hz, 1H), 4.00 (d, $J = 14.0$ Hz, 1H), 3.52 (d, $J = 14.0$ Hz, 1H); 3.44 (m, 1H), 3.30 (m, 1H), 3.07–3.02 (m, 1H), 2.53 (dd, $J = 9.4$, 2.9 Hz), 1.80–1.77 (m, 1H), 1.49–1.46 (m, 1H), 1.29 (d, $J = 6.0$ Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 140.5, 138.8, 136.9, 135.9, 128.2, 128.1, 128.0, 127.8, 127.3, 126.6, 78.1, 70.2, 69.1, 64.0, 61.2, 46.0, 43.9, 17.8 ppm; HRMS (FAB$^+$) (M+H$^+$): calcd for $C_{22}H_{26}NO$ 320.2014, found 320.2015.

3.9. 2′-((3*R*)-2-Ethyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-ylmethyl)-isoindole-1′,3′-dione 6a

Yield: 1.07 g (3.78 mmol, 50%) (yellow oil). $R_f = 0.51$ (MeOH/CH_2Cl_2 1:9); IR (neat) *v* 2970, 1773, 1715, 1394, 913 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87–7.83 (m, 1H), 7.74–7.70 (m, 1H), 6.26–6.23 (m, 1H), 6.08 (dd, $J = 5.6$, 2.0 Hz, 1H), 3.91–3.86 (m, 2H), 3.67 (dd, $J = 13.7$, 10.0 Hz, 1H), 2.73 (m, 1H), 2.49–2.40 (m, 1H), 2.34–2.26 (m, 1H), 1.88–1.82 (m, 2H), 1.43 (m, 1H), 1.18 (t, $J = 7.3$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.4, 136.1, 133.8, 132.4, 132.0, 123.1, 64.4, 62.1, 48.5, 45.9, 45.1, 43.0, 14.6 ppm; HRMS (EI): calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1367.

3.10. 2′-((3*S*)-2-Ethyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-ylmethyl)-isoindole-1′,3′-dione 6b

Yield: 0.71 g (2.52 mmol, 34%) (yellow oil). $R_f = 0.39$ (MeOH/CH_2Cl_2 1:9); IR (neat) *v* 2971, 1772, 1715, 1394, 913 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86–7.84 (m, 2H), 7.74–7.71 (m, 2H), 6.53–6.47 (m, 2H), 3.64–3.59 (m, 2H), 3.38 (dd, $J = 13.6$, 10.7 Hz, 1H), 2.89–2.87 (m, 1H), 2.78–2.63 (m, 3H), 1.75–1.72 (m, 1H), 1.55–1.52 (m, 1H), 1.29 (t, $J = 7.2$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.2, 137.9, 136.5, 133.8, 132.0, 123.1, 66.7, 62.4, 51.4, 45.9, 44.6, 41.8, 14.9 ppm; HRMS (EI): calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1368.

3.11. 2′-((3*R*)-2-Benzyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-ylmethyl)-isoindole-1′,3′-dione 8

Yield: 0.28 g (0.86 mmol, 81%) (light-yellow oil). $R_f = 0.59$ (ethyl acetate/pentane 1:1); IR (neat) *v* 2984, 1773, 1715, 1392, 913 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82–7.91 (m, 2H), 7.71–7.68 (m, 2H), 7.32–7.25 (m, 4H), 7.19–7.15 (m, 1H), 6.38–6.35 (m, 1H), 6.15 (dd, $J = 5.6$, 1.9 Hz, 1H), 3.74 (d, $J = 1.2$ Hz, 1H), 3.74–3.61 (m, 2H), 3.42 (dd, $J = 12.9$ Hz, 2H), 2.74 (d, $J = 1.5$ Hz), 2.12 (dd, $J = 8.2$, 5.6 Hz, 1H), 1.88 (d, $J = 8.5$ Hz, 1H), 1.40 (d, $J = 8.5$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.4, 139.7, 136.6, 133.7, 132.7, 131.9, 128.9, 128.1, 123.1, 64.0, 62.1, 58.5, 46.1, 45.2, 42.5 ppm; HRMS (EI): calcd for $C_{22}H_{20}N_2O_2$ 344.1525, found 344.1525.

3.12. 2′-((3*R*)-2-((1*S*)-Phenylethylamino)-2-azabicyclo-[2.2.1]-hept-5-ene-3-ylmethyl)-isoindole-1′,3′-dione 10

Yield: 0.33 g (0.91 mmol, 74%) (light-yellow oil). $R_f = 0.56$ (ethyl acetate/pentane 1:1); $[\alpha]_D^{22} = -84$ (*c* 3.0, $CHCl_3$); IR (neat) *v* 2979, 1774, 1715, 1392 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75–7.72 (m, 2H), 7.67–7.63 (m, 2H), 7.42–7.35 (m, 4H), 7.28–7.24 (m, 1H), 6.29–6.26 (m, 1H), 6.20 (dd, $J = 5.7$, 1.8 Hz, 1H), 4.22 (d, $J = 1.5$ Hz, 1H), 3.37 (dd, $J = 13.6$, 10.4 Hz, 1H), 3.10 (q, $J = 6.6$ Hz, 1H), 2.97 (dd, $J = 13.6$, 4.4 Hz, 1H), 2.56 (d, $J = 1.5$ Hz), 2.11 (dd, $J = 10.4$, 4.4 Hz, 1H), 1.92 (d, $J = 8.6$ Hz, 1H), 1.44–1.39 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.1, 145.6, 135.9, 133.5, 132.3, 131.8, 128.1, 127.9, 126.9, 122.8, 63.2, 63.0, 61.1, 45.0, 44.2, 42.5, 22.1 ppm; HRMS (EI): calcd for $C_{23}H_{22}N_2O_2$ 358.1681. found 358.1682.

3.13. 2′-((3*R*)-2-((1*S*)-Phenylethylamino)-2-azabicyclo-[2.2.1]-hept-5-ene-3-ylmethyl)-pyrrolidine-1′,3′-dione 13

Yield: 0.27 g (0.87 mmol, 43.5%) (white crystals, from hexane). $R_f = 0.59$ (MeOH/CH_2Cl_2 1:9); mp 116 °C;

$[\alpha]_D^{22} = -33.5$ (c 1.0, $CHCl_3$); IR (neat) ν 1702, 1398, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.23 (m, 5H), 6.30–6.27 (m, 1H), 6.17 (dd, $J = 5.6$, 1.7 Hz, 1H); 4.18–4.17 (m, 1H), 3.21 (dd, $J = 13.2$, 8.4 Hz, 1H), 3.06 (q, $J = 6.5$ Hz, 1H), 2.83 (dd, $J = 13.2$, 4.4 Hz, 1H), 2.53 (s, 1H), 2.47–2.46 (m, 1H), 1.99 (m, 1H), 1.84–1.82 (m, 1H), 1.41–1.39 (m, 1H), 1.36 (d, $J = 6.5$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 177.0, 145.6, 135.8, 132.55, 128.15, 128.0, 127.0, 63.2, 63.1, 69.5, 45.1, 44.4, 43.5, 27.9, 22.2 ppm; HRMS (FAB^+) ($M+H^+$): calcd for $C_{19}H_{23}N_2O_2$ 311.1759, found 311.1756.

3.14. 2′-((3*R*)-2-Benzyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-ylethyl)-isoindole-1′,3′-dione 16

Yield: 0.25 g (0.68 mmol, 52%) (colorless oil). $R_f = 0.40$ (ethyl acetate/pentane 2:8); IR (neat) ν 2985, 1773, 1708, 1386, 1332, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86–7.83 (m, 2H), 7.75–7.71 (m, 2H), 7.42–7.33 (m, 4H), 7.28–7.25 (m, 1H), 6.37–6.35 (m, 1H), 6.18 (dd, $J = 5.7$, 1.8 Hz, 1H), 4.37–4.29 (m, 1H), 3.86 (d, $J = 13.4$ Hz, 1H), 3.63 (d, $J = 1.1$ Hz, 1H), 3.27 (d, $J = 13.4$ Hz, 1H), 2.58 (d, $J = 1.6$ Hz, 1H), 2.48 (d, $J = 10.1$ Hz, 1H), 1.83 (d, $J = 8.4$ Hz, 1H), 1.70 (d, $J = 7.1$ Hz, 3H), 1.30 (d, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.4, 139.7, 136.7, 133.7, 133.6, 131.8, 128.4, 128.1, 126.7, 123.0, 64.5, 62.4, 58.5, 52.7, 45.9, 45.1, 16.8 ppm; HRMS (EI): calcd for $C_{23}H_{22}N_2O_2$ 358.1681, found 358.1682.

3.15. 2′-((1*S*)-(2-Benzyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-yl)-ethyl)-isoindole-1′,3′-dione 17a and 17b

The aldehyde **14** (0.62 g, 3.0 mmol) was dissolved in ~20 ml of CH_2Cl_2 under a nitrogen atmosphere and $MgSO_4$ (1.5 g, 0.5 g/mmol) was added. The reaction mixture was cooled down to 0 °C using an ice bath and benzylamine (0.33 ml, 3.0 mmol) was added. After the imine formation was complete (~2 h by ^1H and ^{13}C NMR) the $MgSO_4$ was filtered off and the solvent was evaporated. The crude imine was redissolved in CH_2Cl_2 (~20 ml) and cooled down in an acetone/dry ice bath to −78 °C followed by addition of $TiCl_4$ (0.33 ml, 3.0 mmol). The freshly distilled cyclopentadiene (0.50 ml, 6.0 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature overnight. The work up and purification were performed as described above. Compounds **17a** and **17b** were obtained in total yield 0.43 g (1.2 mmol, 40%) after purification.

3.16. 2′-((1*S*)-((3*R*)-2-Benzyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-yl)-ethyl)-isoindole-1′,3′-dione 17a

Yield: 0.24 g (0.67 mmol, 22%) (light-yellow oil). $R_f = 0.45$ (ethyl acetate/pentane 2:8); $[\alpha]_D^{22} = +24$ (c 1.0, $CHCl_3$); IR (neat) ν 2924, 2254, 1706, 1381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80–7.66 (m, 2H), 7.60–7.56 (m, 2H), 7.03–6.92 (m, 5H); 6.42–6.40 (m, 1H), 6.28–6.26 (m, 1H), 3.97 (dq, $J = 10.1$, 7.1 Hz, 1H), 3.61 (d, $J = 14.2$ Hz, 1H), 3.47 (dd, $J = 10.1$, 3.0 Hz, 1H), 3.43 (d, $J = 14.2$ Hz, 1H), 3.41–3.40 (m, 1H), 3.18–3.17 (m, 1H), 1.84–1.82 (m, 1H), 1.57–1.55 (m, 1H), 1.44 (d, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.7, 140.5, 138.5, 134.1, 133.4, 131.7, 127.79, 127.78, 126.1, 122.75, 65.63, 65.60, 61.1, 52.1, 46.6, 45.0, 15.9 ppm; HRMS (FAB^+) ($M+H^+$): calcd for $C_{23}H_{23}N_2O_2$ 359.1759, found 359.1757.

3.17. 2′-((1*S*)-((3*S*)-2-Benzyl-2-azabicyclo-[2.2.1]-hept-5-ene-3-yl)-ethyl)-isoindole-1′,3′-dione 17b

Yield: 0.19 g (0.53 mmol, 18%) (light-yellow oil). $R_f = 0.56$ (ethyl acetate/pentane 2:8); $[\alpha]_D^{22} = +2.5$ (c 1.0, $CHCl_3$); IR (neat) ν 2925, 2254, 1078, 1468, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74–7.72 (m, 2H), 7.62–7.59 (m, 2H), 7.04–6.93 (m, 5H), 6.50–6.47 (m, 1H), 6.16 (dd, $J = 5.7$, 2.0 Hz, 1H); 4.27 (dq, $J = 10.1$, 7.1 Hz, 1H), 3.57–3.56 (m, 1H), 3.29 (d, $J = 14.2$ Hz, 1H), 3.14 (d, $J = 14.2$ Hz, 1H), 2.91–2.90 (m, 1H), 2.47 (d, $J = 10.1$ Hz, 1H), 1.92–1.90 (m, 1H), 1.56 (d, $J = 7.1$ Hz, 3H), 1.39–1.36 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 168.7, 139.8, 136.6, 134.0, 133.5, 131.8, 127.8, 127.7, 126.1, 122.8, 66.2, 63.1, 58.4, 52.5, 46.7, 45.4, 16.1 ppm; HRMS (FAB^+) ($M+H^+$): calcd for $C_{23}H_{23}N_2O_2$ 359.1759, found 359.1762.

3.18. 2′-(2-Benzyl-2-azabicyclo-[2.2.1]-hept-6-ene-3-yl)-pyrrolidine-1′-carboxylic acid *tert*-butyl ester 19 (mixture of diastereomers)

Yield: 0.28 mg (0.79 mmol, 70%) (yellow oil). $R_f = 0.62$ ($MeOH/CH_2Cl_2$ 1:9); IR (neat) ν 2975, 2936, 1683, 1393, 1365, 1170, 1103, 911 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.23 (m), 6.45–6.43 (m), 6.08–6.03 (m), 4.10 (br s), 3.90 (br s), 3.69–3.09 (m), 2.70–2.66 (m), 2.00–1.75 (m), 1.47 (s), 1.26 (s) ppm; HRMS (EI): calcd for $C_{22}H_{30}N_2O_2$ 354.2307, found 354.2306.

Acknowledgement

This work was supported by grants from The Swedish Research Council.

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