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The aza-Diels–Alder reaction protocol—a useful approach to chiral, sterically constrained α-amino acid derivatives

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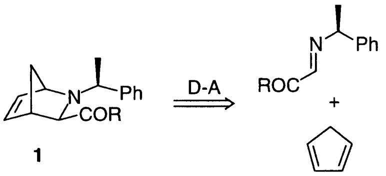
Abstract—Different types of polycyclic α-amino acid derivatives are prepared from chiral imines by using well-established aza-Diels–Alder reaction conditions. Simply by varying the diene moiety, different products such as spirocyclic compounds **8** and **9**, anthracene **10**, and tetrahydroquinolines **15–21** are formed. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

α-Amino acids can be found almost anywhere in nature, most evident as the building blocks of peptides and proteins but also extensively in other natural products.[1] In the area of organic synthesis, α-amino acids are one of the most frequently used sources of chirality. The use of both natural and unnatural α-amino acids and their derivatives as chiral reagents, auxiliaries, and ligands for asymmetric catalysis is widely spread.[2,3a] This has resulted in the development of a vast number of methods for the asymmetric synthesis of nonproteinogenic α-amino acids.[3] Among these, the asymmetric aza-Diels–Alder reaction of imines provide an effective route to optically active, sterically constrained α-amino acid derivatives.[4–6] Conformationally restricted amino acids, precursors to β-amino alcohols, are highly interesting synthetic targets since they are valuable as chiral inducers in different asymmetric transformations.

Since 1996, we have focused part of our research on the sterically constrained 2-aza-norbornene derivative **1** (Scheme 1).[7] As the chiral auxiliary ((*S*)-(−)- or (*R*)-(+)-1-phenylethylamine) used in the synthesis is available in both enantiomeric forms at equal cost, either of the enantiomers of **1** are as easily obtained.



Scheme 1. 2-Aza-norbornene derivatives made via a Diels–Alder reaction.

Dialkyltartrate serves as precursor for the imine dienophile. An oxidative cleavage of the tartrate produces alkylglyoxylate, which is reacted with (*S*)- or (*R*)-1-phenylethylamine to obtain the chiral imine. Aza-bicyclo[2.2.1]heptene derivative **1** is then formed by treating protonated imine with a diene, here cyclopentadiene.[8] The Diels–Alder adduct **1** has, after different modifications, been used with great success in a variety of reactions, e.g. diethylzinc additions to imines and aldehydes, transfer hydrogenation of ketones, and rearrangement of *meso*-epoxides (Fig. 1).[7]

The first step in the modification of the aza-Diels–Alder adduct is a hydrogenation and/or a debenzylation reaction (Scheme 2, **2** and **3**). Under hydrogenation conditions, hydrogenolytic cleavage of the strained allylic C–N bond could occur as a side reaction to produce highly useful α-amino esters **4** or **5** (Scheme 2). For the protocol to be synthetically useful, reaction conditions were developed to obtain each of the four possible amino esters as sole products (Scheme 2).[9] The acid-catalysed allylic cleavage is avoided by neutralising traces of acid in the reaction medium by addition of base. At the high hydrogen pressure needed for the preparation of **3**, the olefin hydrogenation seem to be fast enough to suppress the allylic cleavage without using base as additive. With addition of acid to the reaction, the rate of allylic C–N cleavage increases, leading to exclusive formation of ring-opened products **4** or **5**. By the use of iminoketones the above strategy can also be extended to the synthesis of different optically active α-amino ketones.

A broad range of imines can be used as dienophiles in the aza-Diels–Alder reaction. Some earlier work in this area made in our research group is summarised in Table 1.

Keywords: α-amino acid; aza-Diels–Alder reaction; anthracene; tetrahydroquinoline.

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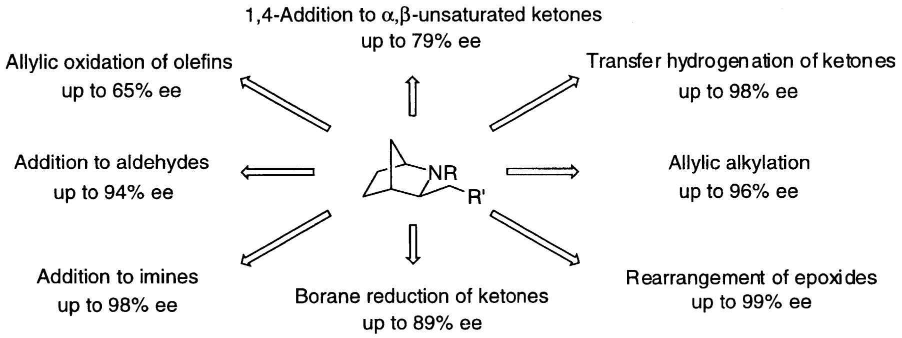
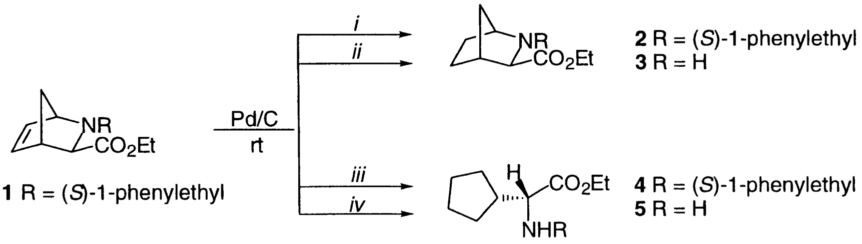
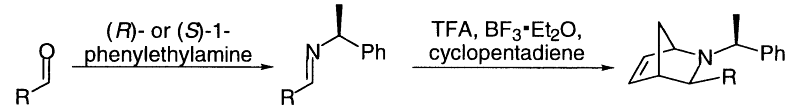


Figure 1. Versatility of the 2-aza-norbornane structure as chiral ligand.[7]



Scheme 2. (*i*) H_2 (1 atm), 1 equiv K_2CO_3, EtOH (**2**); (*ii*) H_2 (7 atm), EtOH (**3**); (*iii*) H_2 (1 atm), HOAc (**4**); (*iv*) H_2 (1 atm), 10 equiv HOAc, MeOH (**5**).

Table 1. Exploring different imines in the asymmetric aza-Diels–Alder reaction[9,10]



Entry	R	Yield (%)[a]	*exo*/*endo* selectivity[b]	d.r.[b,c]	References
1	EtO_2C	70	>99:2	90:10	10a
2	BnO_2C	83	>99:1	97:3	10b
3	PhCO	42	95:5	83:17	9
4	2-Pyridyl	80	>99:1	87:13	10c
5	4-Pyridyl	60	>99:1	80:20	10c
6	2-Quinolnyl	80	>99:1	90:10	10c
7	4-Quinolnyl	79	>99:1	90:10	10c
8	2-Imidazoyl	60	>99:1	75:25	10c
9	2-Thiazoyl	80	>99:1	90:10	10c
10	Pyrrolidine-1-carbonyl	40	95:5	80:20	10d
11	Piperidine-1-carbonyl	29	96:4	80:20	10d
12	Morpholine-1-carbonyl	14	95:5	79:21	10d

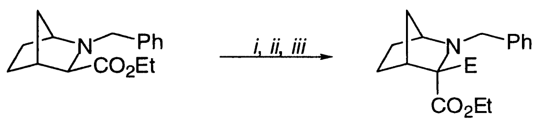
[a] Isolated yield.
[b] Determined by NMR spectroscopy on the crude reaction mixture.
[c] Diastereomeric ratio of *exo*-isomers.

Using this type of dienophile, the *exo*/*endo* selectivity is generally as high as >98:2 in favour of the *exo*-isomer (Table 1).[4a] Also the selectivity between the two *exo*-isomers is high, typically about 90:10 (Table 1), and the pure diastereomers can easily be obtained using flash chromatography.

Access to a more extensive amount of the *endo*-isomer was given as a synthetic route to invert the stereochemistry at C-3 in the aza-norbornyl skeleton was developed.[11] Deprotonation, followed by a selective electrophile addition produce the *endo*-isomer in yields up to 90% and selectivity up to >98%. A range of electrophiles (E^+, Table 2) can be used in the reaction, e.g. water, methyl iodide, and benzaldehyde.

When imines derived from aromatic amines are used in the Diels–Alder reaction, the imine turns to act as a diene instead of a dienophile. To induce stereoselectivity in the reaction, an optically active glyoxylate can be used for formation of imine. The concept of using such chiral heterodienes has been much less explored than the chiral heterodienophile approach.[4,12] Under acidic conditions, the diene adds to a number of electron rich dienophiles, such as cyclopentadiene, cyclohexadiene, dihydrofuran, and indene, to afford different tetrahydroquinolines.[13] Trace amounts of aza-norbornene product is obtained in some of the reactions. The tetrahydroquinoline backbone is frequently observed in natural products[14] and is found in numerous commercial products, including pharmaceuticals, fragrances and dyes.[15] Derivatives have been found to

Table 2. Different electrophiles in the addition to aminoesters



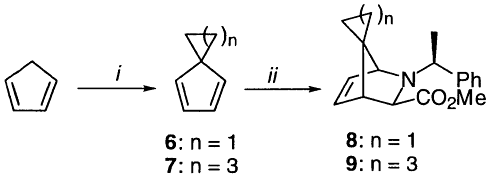
Entry	E^+	E	Selectivity (%)	Yield (%)
1	H_2O	H	70	90
2	CH_3I	CH_3	>98	80
3	C_3H_5Br	C_3H_5	>98	67
4	C_6H_5CHO	C_6H_5CHOH	>98	68
5	CH_3OCOCl	CH_3OCO	>98	75

(*i*) LDA, −20°C; (*ii*) E^+; (*iii*) H_2O.

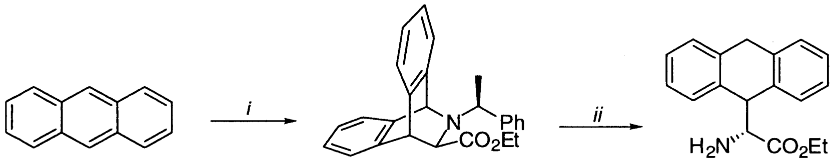
exhibit, e.g., antitumour activities and can also act as potent antipsycotic agents.[16]

2. Results and discussion

Most of our earlier research has been concentrated on how to modify the chiral imine dienophile to extend the scope of the aza-Diels–Alder reaction. We now focus on the diene moiety[17] in the search for rigid amino acid derivatives suitable as building blocks in asymmetric synthesis. Our first interest was dienes having a spiro-cyclic skeleton. The resulting increased steric bulk at the 1-carbon bridge in the Diels–Alder adduct would open up for a new group of structures with potential in various fields of asymmetric catalysis. Spiro-dienes **6** and **7** were synthesised by the coupling of cyclopentadiene with a dihaloalkane (Scheme 3).[18] All attempts to synthesise spiro[3.4]octa-5,7-diene (n=2, Scheme 3) and spiro[4.5]deca-1,3-diene (n=4, Scheme 3) failed, which is in accordance with results published earlier by others.[19] The spiro-dienes were used in the aza-Diels–Alder reaction to obtain spiro-aminoesters **8** and **9** (Scheme 3).[8] The yield in the cycloaddition reaction of **6** and **7** are generally low, probably due to the high tendency for diene polymerisation in acidic reaction medium.



Scheme 3. (*i*) n=1: NaOH, 1,2-dichloroethane, *tetra-n*-butylammonium iodide, rt, overnight; n=3: NaH, 1,4-dibromobutane, THF, rt; (*ii*) ((*R*)- or (*S*)-1-phenylethylimino)-acetic acid methyl ester, TFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C to rt.



10 **11**

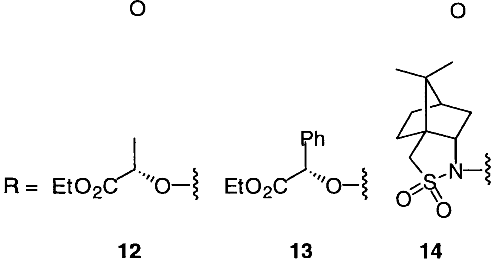
Scheme 4. (*i*) ((*S*)-1-phenylethylimino)-acetic acid methyl ester, TFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C to rt, overnight; (*ii*) H_2 (500 psi), $Pd(OH)_2$, EtOH, 7 days.

Next, we turned to dienes that would not only increase the steric bulk but also change the electronic properties of the bicyclic structure. Anthracene and its derivatives undergo Diels–Alder reactions with a number of different dienophiles.[20] Yet, this group of dienes has not, to our knowledge, been used in combination with a chiral imine dienophile before. Due to the rather electron-poor character of anthracene, a reaction with an electron deficient imine is likely to be more sluggish than for cyclopentadiene. This is evident, as only a moderate yield of **10** (Scheme 4) was isolated after treating anthracene with ((*S*)-1-phenylethylimino)-acetic acid ethyl ester and acids.[8]

The highly constrained aza-Diels–Alder adduct **10** can be further elaborated to form the ring-opened product **11** by treatment with $Pd(OH)_2$ under H_2.[21] The weaker *endo*-cyclic benzylic bond is hydrogenolysed first to form N-protected **11** which is deprotected after further treatment with H_2. Due to the lower reactivity of the *exo*-cyclic benzylic bond in the structure, it was not possible to isolate any N-deprotected **10** (Scheme 4).

As mentioned earlier, chiral aromatic imines are efficient precursors in the synthesis of tetrahydroquinolines[13]—the third class of amino acid derivatives included in the study. Our main goal in this well explored area was to apply and evaluate ethyl lactate, ethyl mandelate and camphorsultam as chiral auxiliaries for the synthesis of optically active tetrahydroquinolines.[22] Of these, ethyl lactate have the great advantage of being highly accessible at low cost. Others have used a similar strategy for making chiral quinoline derivatives but with the help of more expensive chiral auxiliaries, e.g. (−)-8-phenylmenthol.[13d]

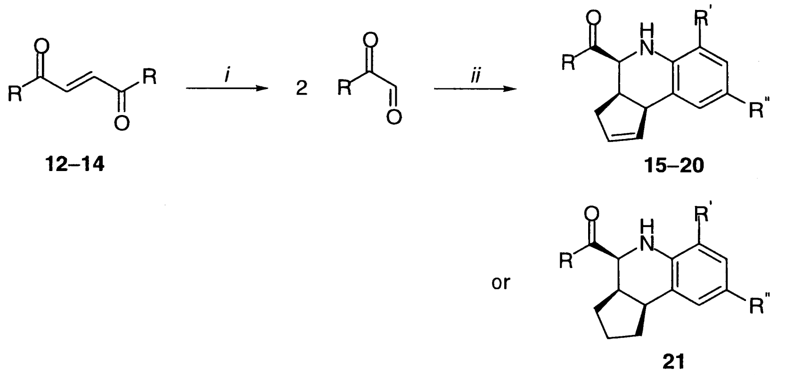
The imine precursors were synthesised by coupling of fumaryl chloride with different chiral auxiliaries to form



12 **13** **14**

Scheme 5. (*i*) **12**: (*S*)-(−)-ethyl lactate, 110°C, overnight; **13**: (*S*)-(+)-ethyl mandelate, 110°C, overnight; **14**: (1*S*,2*R*)-(−)-2,10-camphorsultam, NaH, toluene, rt, overnight.

Table 3. Synthesis of tetrahydroquinolines **15–21**



12–14

15–20

21

entry	diester/diamide[a]	amine	product	%yield[b]	d.r.[c]
1	**12**	4-MeO-aniline	**15**	59	82:18
2	**12**	aniline	**16**	62	84:16
3	**12**	2-Et-aniline	**17**	44	83:17
4	**12**	2-*i*Pr-aniline	**18**	64	87:13
5	**13**	4-MeO-aniline	**19**	64	85:15
6	**14**	4-MeO-aniline	**20**	49	84:16
7	**12**	4-MeO-aniline	**21**	38	74:26

(*i*) O_3, CH_2Cl_2, −78°C then Me_2S, −78°C to rt overnight; (*ii*) amine, MS 4 Å, CH_2Cl_2, rt, 6 h, then TFA, $BF_3{\cdot}Et_2O$, and cyclopentadiene (entry 1–6) or cyclopentene (entry 7), −78°C to rt overnight.

[a] See Scheme 5.

[b] Isolated.

[c] Determined on the crude reaction mixture by NMR spectroscopy.

the diesters **12** and **13**, and the diamide **14** (Scheme 5). The fumaryl derivatives were then oxidatively cleaved by ozone to the corresponding glyoxylates, which were converted to imine by treatment with different aniline derivatives. Without isolation of the imine, using the same protocol as for the synthesis of **1** and **8–10**, the reaction mixture was acidified and cyclopentadiene or cyclopentene was added to furnish tetrahydroquinolines **15–21** (Table 3). To verify the diastereoselectivity obtained in the cycloadditions (Table 3), the enantiomeric excess of the corresponding amino alcohols was determined (HPLC). The relative stereochemistry of **15–21** were assigned according to the literature.[13]

The cycloadducts were obtained in moderate to high yields and with diastereoselectivity ranging from 74:26 to 87:13 (Table 3). Enantioselectivity up to 92% was observed when measured on amino alcohols from purified **15–21** (flash chromatography). This clearly shows the possibility of separating the diastereomers formed by simple flash chromatography. When using (*S*)-ethyl lactate as chiral auxiliary, cyclopentadiene is acting as a better dienophile compared to cyclopentene (cf. entries 1 and 7, Table 3). The addition of steric bulk to the imine seems not to affect the reaction significantly (cf. entries 2–4). Also, no obvious correlation between electronic properties of the diene, reactivity, and selectivity was observed (cf. entries 1, 5–7 with 2–4). Evident from the results is that the cheap (*S*)-ethyl lactate works just as well as chiral auxiliary as the more elaborate (1*S*,2*R*)-(−)-2,10-camphorsultam structure. Even though the obtained stereoselectivity is slightly lower than that reported using (−)-8-phenylmenthol as chiral inducer,[13d] the low cost of (*S*)-ethyl lactate makes our route highly competitive.

3. Conclusion

Two new types of bicyclic aza-Diels–Alder adducts have been synthesised. Spiro-structures **8** and **9** provide the possibility to investigate the influence of steric bulk from the 1-carbon-bridge which has not been possible before. Anthracene derivative **10** can be used for evaluation of increased in steric bulk and electronic effects on, e.g., ligand performance. We have also presented an enantioselective route to tetrahydroquinolines using chiral auxiliaries available at low cost.

4. Experimental

4.1. General

All reactions were run under argon or nitrogen using dry glassware and magnetic stirring. THF was freshly distilled from a deep-blue solution of sodium-benzophenone ketyl under nitrogen. CH_2Cl_2 was distilled from powdered CaH_2 under nitrogen just prior to use. Flash chromatography was performed using Matrex silica gel 60 Å (37–70 μm). Analytical TLC was carried out utilising 0.25 mm precoated plates from Merck, silica gel 60 UV_{254} and spots were visualised by the use of UV light and ethanolic phosphomolybdic acid followed by heating. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or a Varian Unity 400 spectrometer at ambient temperature for $CDCl_3$ solutions. Chemical shifts for protons are reported using the residual $CHCl_3$ as internal reference (δ 7.26). Carbon signals are referred to the shift from the ^{13}C signal of $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a

Perkin–Elmer 1760 FT-IR spectrometer. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Mass spectra were recorded using a Finnigan MAT GCQ PLUS system (EI; 70 eV).

4.1.1. Spiro[2.4]hepta-4,6-diene (6). Diene **6** was synthesised using a slightly modified literature procedure.[18a] NaOH (25.9 g, 648 mmol), *tetra-n*-butylammonium iodide (1.40 g, 3.83 mmol), cyclopentadiene (15 mL, 181 mmol), and 1,2-dichloroethane (13 mL, 165 mmol) were stirred for 8 h. A solution of THF and H_2O (1/1, 50 mL) was added and the resulting mixture was poured onto an ice/water slurry. The organic layer was separated and the aqueous phase extracted with pentane (2×200 mL). The combined organic layers were washed with 0.5 M HCl (50 mL), water (2×50 mL) and dried ($MgSO_4$). After distillation (35–40°C, 10 mmHg), **6** was obtained (3.5 g, 23%). Spectroscopic and physical data were in complete agreement with those published.[23]

4.1.2. Spiro[4.4]nona-1,3-diene (7). Diene **7** was synthesised using a literature method.[18b] Physical and spectroscopic data were in complete agreement with those published.[24]

4.1.3. Cycloadduct with spiro[2.4]hepta-4,6-diene (8). To dimethyl-(L)-tartrate (6.03 g, 33.7 mmol) in Et_2O (80 mL) at 0°C was added periodic acid (7.65 g, 33.7 mmol) in small portions during 20 min. The reaction mixture was then stirred at room temperature for 1 h. After drying ($MgSO_4$), the ether solution was filtered through Celite™, and concentrated in vacuo. The residual was dissolved in CH_2Cl_2 (100 mL), activated MS 4 Å was added and the reaction mixture was cooled to 0°C. (*R*)-1-Phenylethylamine (8.62 mL, 67.3 mmol) was added dropwise via syringe. After stirring for 30 min, the reaction was cooled further to −78°C and TFA (5.10 mL, 67.3 mmol), $BF_3{\cdot}OEt_2$ (8.53 mL, 67.3 mmol) and **6** (6.20 g, 67.3 mmol) were added dropwise. The reaction mixture was then stirred over night while the temperature was allowed to rise slowly to rt. To quench the reaction, $NaHCO_3$ (aq. sat., 100 mL) was added. The organic layer was separated and subsequently washed with brine (100 mL) and dried ($MgSO_4$). After concentration in vacuo, the crude product was obtained as a 4:3 mixture of the two *exo*-isomers (95%, 18.0 g, 63.6 mmol). Purification was performed using flash chromatography (silica gel deactivated with Et_3N, pentane/EtOAc, 9:1 to 4:1) to afford the major *exo*-isomer in 32% yield from dimethyl-(L)-tartrate (6.0 g, 21 mmol). **8**: R_f 0.50 (pentane/Et_2O 5:1); $[\alpha]_D^{23}=+59.9$ (c=3.83, CH_2Cl_2); IR (film, cm^{-1}) 3065, 3026, 2963, 1737; ^1H NMR (400 MHz) δ 7.36–7.24 (5H, m), 6.43 (1H, dd, J=5.2, 2.4 Hz), 6.39 (1H, m), 6.07 (1H, dd, J=5.2, 1.7 Hz), 3.74 (3H, s), 3.66 (1H, q, J=6.6 Hz), 3.30 (1H, m), 2.05 (1H, m), 1.70–1.64 (1H, m), 1.60–1.45 (2H, m), 1.35 (3H, d, J=6.6 Hz), 1.33–1.28 (1H, m); ^{13}C NMR (100.4 MHz) δ 174.1, 145.3, 144.4, 140.0, 128.5, 127.8, 127.3, 127.1, 127.0, 56.9, 55.4, 51.9, 37.7, 24.7, 13.5, 13.2; MS (GC) m/z (rel. intensity) 284 ($M+H^+$, 19), 224 (100), 163 (6), 120 (69), 105 (96), 93 (69), 77 (28); Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.02; H, 7.27; N, 5.03.

4.1.4. Cycloadduct with spiro[4.4]nona-1,3-diene (9). The procedure described for **8** was followed, using dimethyl (L)-tartrate (0.92 g, 5.17 mmol), (*S*)-1-phenylethylamine (1.32 mL, 10.3 mmol), and **7** (1.50 g, 12.5 mmol), which gave **9** as a mixture of diastereomers (major *exo*/minor *exo*/*endo*, 70:20:10). Purification was performed using flash chromatography (silica gel deactivated with Et_3N, pentane/EtOAc, 95:5) to obtain the major *exo*-isomer as a white solid in 34% yield (1.1 g). **9**: mp 94–95°C; $[\alpha]_D^{25}=+78.4$ (c=0.92, CH_2Cl_2); IR (KBr, cm^{-1}) 3045, 2978, 1710; ^1H NMR (400 MHz) δ 7.36 (2H, dd, J=7.1, 1.4 Hz), 7.24 (2H, dt, J=7.1, 1.6 Hz), 7.17 (1H, m), 6.46 (1H, m), 6.20 (1H, m), 3.75 (1H, m), 3.33 (3H, s), 3.27 (1H, q, J=6.6 Hz), 2.77 (1H, m), 2.43 (1H, m), 2.20–2.12 (1H, m), 1.62–1.21 (6H, m), 1.39 (3H, d, J=6.6 Hz), 1.12 (1H, dt, J=13.7, 8.5 Hz); ^{13}C NMR (100.4 MHz) δ 173.1, 144.0, 136.9, 133.6, 128.7, 127.5, 126.9, 69.6, 66.4, 56.5, 51.1, 46.9, 33.4, 31.4, 26.4, 25.1, 21.0, 18.9; MS (GC) m/z (rel. intensity) 312 (M+H, 5), 296 (3), 252 (72), 206 (7), 148 (100); Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.96; H, 8.12; N, 4.32.

4.1.5. Cycloadduct with anthracene (10). The procedure described for **8** was followed using diethyl-(L)-tartrate (1.50 g, 7.30 mmol), (*S*)-1-phenylethylamine (1.87 mL, 14.6 mmol) and anthracene (3.25 g, 18.2 mmol, added as solid), which gave **10** as a mixture of two diastereomers (57:43, 6.7 g). The crude product was purified by flash chromatography (silica, pentane/EtOAc, 90:10) to afford pure major diastereomer in 37% yield (2.1 g, 5.3 mmol). **10**: R_f 0.25 (pentane/EtOAc 9:1); mp 105–106°C; $[\alpha]_D^{25}=+23.1$ (c=1.06, $CHCl_3$); IR (film, cm^{-1}) 3425, 1752, 1718; ^1H NMR (300 MHz) δ 7.32–7.44 (3H, m), 7.05–7.24 (10H, m), 5.39 (1H, s), 4.42 (1H, d, J=2.5 Hz), 3.74 (2H, q, J=7.1 Hz), 3.11 (1H, d, J=2.5 Hz), 2.97 (1H, q, J=6.5 Hz), 1.52 (3H, d, J=6.5 Hz), 0.90 (3H, t, J=7.1 Hz); ^{13}C NMR (75.3 MHz) δ 172.3, 144.5, 142.6, 141.0, 140.0, 128.1, 128.0, 127.0, 126.4, 126.35, 126.27, 126.0, 124.0, 123.9, 123.8, 66.2, 64.1, 60.2, 59.5, 47.8, 21.6, 14.0; Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.28; H, 6.41; N, 3.51.

4.1.6. (1*R*)-Amino-(9,10-dihydro-anthracen-9-yl)-acetic acid ethyl ester (11). Dry $Pd(OH)_2/C$ (20%, 0.40 g wet weight) was added to **10** (0.50 g, 1.30 mmol), dissolved in EtOH (25 mL). The mixture was stirred under H_2 at 500 psi at room temperature for 7 days. The catalyst was removed by filtration through Celite™, and the filtrate was evaporated in vacuo. The crude product was purified by flash chromatography (silica, Et_2O) to afford **11** (0.3 g, 81%) as a white solid. All spectroscopic and physical data were in complete agreement with the reported for the racemic compound.[21] $[\alpha]_D^{25}=+35.2$ (c=1.22, $CHCl_3$).

4.1.7. Bis[(*S*)-1-(ethoxycarbonyl)ethyl] fumarate (12). Fumarate **12** was prepared from (*S*)-ethyl lactate and fumaryl chloride according to a literature procedure.[25] All spectroscopic and physical data were in agreement with the data for the commercial available compound.

4.1.8. Bis[(*S*)-1-(ethoxycarbonyl)-1-(phenyl)methyl] fumarate (13). Compound **13** was prepared from (*S*)-ethyl mandelate and fumaryl chloride according to a literature procedure.[25] **13**: IR (KBr, cm^{-1}) 3067, 2983, 1719, 1646;

^{1}H NMR (200 MHz) δ 7.59–7.31 (m, 10H), 7.07 (s, 2H), 6.02 (s, 2H), 4.20 (q, 4H, J=7.0 Hz), 1.23 (6H, t, J=7.0 Hz); ^{13}C NMR (50.2 MHz) δ 168.1, 163.9, 133.6, 133.3, 129.4, 128.8, 127.6, 75.3, 61.9, 13.9; MS (GC) *m/z* (rel. intensity) 440 (M$^+$, <1), 216 (35), 164 (98), 163 (100), 135 (48), 91 (31); Anal. Calcd for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.46; H, 5.50.

4.1.9. (−)-*N*,*N*′-Fumaroylbis[(2*R*)-bornane-2, 10-sultam] (14). Compound **14** was prepared from (1*S*)-(−)-2,10-camphorsultam and fumaryl chloride according to a literature procedure.[26] All spectroscopic and physical data were in complete agreement with the reported.[27]

4.1.10. (3a*R*,4*S*,9b*R*)-8-Methoxy-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylic acid (1*S*)-1-ethoxycarbonyl ethyl ester (15). Fumarate **12** (2.40 g, 7.60 mmol) was dissolved in CH_2Cl_2 (120 mL). After cooling to −78°C, O_3 was bubbled through the solution until a blue colour persisted (2 h). The reaction was quenched via dropwise addition of Me_2S (3.35 mL, 45.6 mmol) in CH_2Cl_2 (4.0 mL). The mixture was allowed to warm up to room temperature over night and then evaporated. The product formed was used without further purification. *p*-Anisidine (2.02 g, 16.4 mmol) was dissolved in CH_2Cl_2 (25 mL), MS 3 Å were added and the atmosphere was changed to N_2. The product from the ozonolysis was added via syringe as a solution in CH_2Cl_2 (25 mL). The reaction mixture was stirred in room temperature for 6 h and then cooled to −78°C. TFA (1.26 mL, 16.3 mmol), $BF_3\cdot OEt_2$ (2.07 mL, 16.3 mmol) and cyclopentadiene (1.62 mL, 19.6 mmol) were added via syringe. The temperature was kept at −78°C for 3 h and then allowed to reach room temperature overnight. $NaHCO_3$ (aq. sat.) was added until the water phase was slightly basic. The reaction mixture was filtrated through Celite™ whereafter the organic phase was dried ($MgSO_4$), filtered and evaporated to dryness. The diastereomeric ratio of the crude product was determined by integration of ^{13}C NMR spectral lines. Purification by flash chromatography (silica gel deactivated with Et_3N, pentane/EtOAc, 6:1) gave **15** as a yellow oil (3.1 g, 59% from **12**). **15**: IR (CH_2Cl_2, cm^{-1}) 3389, 1755, 1727, 1095, 1041; ^{1}H NMR (200 MHz) δ 6.63–6.57 (m, 3H), 5.78–5.65 (m, 2H), 5.18 (q, 1H, J=7.0 Hz), 4.23 (q, 2H, J=7.0 Hz), 4.16–4.08 (m, 1H), 4.08–4.01 (m, 1H), 3.95 (br s, 1H), 3.73 (s, 3H), 3.48–3.26 (m, 1H), 2.52 (dd, 2H, J=1.5, 8.9 Hz), 1.54 (d, 3H, J=7.0 Hz), 1.30 (t, 3H, J=7.0 Hz), ^{13}C NMR (50.2 MHz) δ 171.1, 169.9, 152.7, 137.2, 133.2, 130.0, 126.7, 116.4, 113.3, 111.9, 68.7, 61.0, 56.3, 55.1, 46.4, 40.3, 32.1, 16.5, 13.7; MS (GC) *m/z* (rel. intensity) 345 (M$^+$, 48), 201 (38), 200 (100), 185 (12), 169 (14); Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.91; H, 6.75; N, 4.05.

4.1.11. (3a*R*,4*S*,9b*R*)-3a,4,5,9b-Tetrahydro-*H*-cyclopenta[*c*]quinoline-4-carboxylic acid (1*S*)-1-ethoxycarbonyl-ethyl ester (16). By following the procedure reported for **15** using **12** (1.51 g, 4.80 mmol), aniline (1.03 mL, 11.3 mmol) and cyclopentadiene (1.12 mL, 13.5 mmol), afforded **16** as a pale yellow solid (1.9 g, 62% from **12**). **16**: IR (CH_2Cl_2, cm^{-1}) 3399, 1755, 1730, 1097; ^{1}H NMR (200 MHz) δ 7.07–6.93 (m, 2H), 6.79–6.56 (m, 2H), 5.82–5.61 (m, 2H), 5.19 (q, 1H, J=7.0 Hz), 3.52–3.30 (m, 1H), 2.62–2.50 (m, 2H), 1.55 (d, 3H, J=7.0 Hz), 1.30 (t, 3H, J=7.0 Hz); ^{13}C NMR (50.2 MHz) δ 171.2, 170.0, 143.5, 133.6, 129.9, 128.4, 126.1, 125.6, 119.0, 115.5, 68.9, 61.2, 56.0, 46.1, 40.7, 32.3, 16.7, 13.9; MS (GC) *m/z* (rel. intensity) 315 (M$^+$, 36), 171 (46), 170 (100), 169 (23), 168 (30); Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.40; H, 6.67; N, 4.28.

4.1.12. (3a*R*,4*S*,9b*R*)-6-Ethyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylic acid (1*S*)-1-ethoxycarbonyl-ethyl ester (17). Following the same procedure as reported for **15** using **12** (1.47 g, 4.66 mmol), 2-ethylaniline (0.86 mL, 6.99 mmol) and cyclopentadiene (0.69 mL, 8.38 mmol), yielded **17** as a pale yellow oil (1.4 g, 44% from **12**). **17**: IR (CH_2Cl_2, cm^{-1}) 3420, 2965, 2939, 1745; ^{1}H NMR (200 MHz) δ 6.97 (app. d, 2H, J=7.6 Hz), 6.77 (app. t, 1H, J=7.6 Hz), 5.86–5.66 (m, 2H), 5.24 (q, 1H, J=7.0 Hz), 4.38–4.13 (m, 5H), 3.62–3.37 (m, 1H), 2.75–2.40 (m, 4H), 1.62 (d, 3H, J=7.0 Hz), 1.42–1.25 (m, 6H); ^{13}C NMR (50.2 MHz) δ 171.5, 170.0, 141.1, 134.0, 129.8, 128.2, 126.2, 125.3, 125.2, 118.5, 69.0, 61.3, 56.0, 46.6, 40.7, 32.3, 23.3, 16.7, 13.9, 12.8; MS (GC) *m/z* (rel. intensity) 343 (M$^+$, 54), 199 (52), 198 (100), 170 (31), 169 (45); Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.82; H, 7.44; N, 4.26.

4.1.13. (3a*R*,4*S*,9b*R*)-6-Isopropyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylic acid (1*S*)-1-ethoxycarbonyl-ethyl ester (18). Following the procedure reported for **15** using **12** (1.50 g, 4.74 mmol), 2-isopropylaniline (1.57 mL, 11.1 mmol) and cyclopentadiene (1.11 mL, 13.4 mmol), gave **18** as a pale yellow solid (2.2 g, 64% from **12**). **18**: IR (CH_2Cl_2, cm^{-1}) 3425, 1755, 1744, 1098; ^{1}H NMR (200 MHz) δ 7.08–6.90 (m, 2H), 6.79 (app. t, 1H, J=7.6 Hz), 5.83–5.65 (m, 2H), 5.23 (q, 1H, J=7.0 Hz), 4.47–4.08 (m, 5H), 3.58–3.36 (m, 1H), 3.12–2.86 (m, 1H), 2.62 (app. d, 2H, J=8.5 Hz), 1.59 (d, 3H, J=7.0 Hz), 1.40–1.24 (m, 9H); ^{13}C NMR (50.2 MHz) δ 171.4, 169.9, 140.5, 134.0, 132.8, 129.8, 126.0, 125.6, 122.2, 118.5, 68.9, 61.1, 56.1, 46.8, 40.6, 32.3, 26.9, 22.3, 21.9, 16.6, 13.9, 13.8; MS (GC) *m/z* (rel. intensity) 357 (M$^+$, 37), 213 (48), 212 (100), 171 (31), 170 (66); Anal. Calcd for $C_{21}H_{27}NO_4\cdot 0.6\ H_2O$: C, 68.49; H, 7.72; N, 3.80. Found: C, 68.35; H, 7.53; N, 3.90.

4.1.14. (3a*R*,4*S*,9b*R*)-8-Methoxy-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylic acid (1*S*)-1-ethoxycarbonyl-phenyl-methyl ester (19). By following the same procedure as reported for **15** using **13** (4.81 g, 10.9 mmol), *p*-anisidine (2.49 g, 20.2 mmol), and cyclopentadiene (2.01 mL, 24.3 mmol), **19** was afforded as a yellow oil (5.7 g, 64% from **13**). **19**: IR (CH_2Cl_2, cm^{-1}) 3375, 1746, 1505, 1229, 1042; ^{1}H NMR (200 MHz) δ 7.62–7.25 (m, 5H), 6.70–6.51 (m, 3H), 6.05 (s, 1H), 5.82–5.66 (m, 2H), 4.33–4.01 (m, 5H), 3.64 (s, 3H), 3.59–3.28 (m, 1H), 2.86–2.61 (m, 2H), 1.21 (t, 3H, J=7.0 Hz); ^{13}C NMR (50.2 MHz) δ 171.1, 167.9, 152.6, 137.2, 133.2, 133.1, 129.9, 128.8, 128.3, 127.9, 127.1, 126.5, 126.1, 116.3, 113.3, 111.8, 74.4, 61.2, 56.3, 54.9, 46.3, 40.3, 32.2, 13.4; MS (GC) *m/z* (rel. intensity) 255 (87), 227 (100), 192 (57), 165 (54); Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.59; H, 6.25; N, 3.28.

4.1.15. (3a*R*,4*S*,9b*R*)-(10,10-Dimethyl-3,3-dioxo-3$^{\lambda 6}$-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-(8-methoxy-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-yl)methanone (20). Following the procedure reported for **15** using **14** (1.70 g, 3.33 mmol), *p*-anisidine (0.87 g, 7.07 mmol), and cyclopentadiene (0.69 mL, 8.39 mmol), yielded **20** as a pale yellow solid (1.4 g, 49% from **14**). **20**: IR (CH$_2$Cl$_2$, cm^{-1}) 3376, 2887, 1710, 1343, 1039; ^{1}H NMR (200 MHz) δ 6.65–6.53 (m, 3H), 5.81–5.64 (m, 1H), 5.63–5.57 (m, 1H), 4.65 (app. d, 1H, J=3.05 Hz), 4.20–4.02 (m, 1H), 4.00–3.87 (m, 1H), 3.69 (s, 3H), 3.58–3.25 (s, 4H), 2.74–2.50 (m, 2H), 2.22–1.60 (m, 5H), 1.42–1.19 (m, 2H), 1.14 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (50.2 MHz) δ 172.0, 152.6, 137.0, 133.6, 129.1, 126.7, 116.9, 113.1, 112.0, 64.6, 58.0, 55.1, 52.4, 48.1, 47.3, 46.5, 44.0, 41.3, 37.8, 31.9, 31.3, 26.0, 20.1, 19.3; MS (GC) m/z (rel. intensity) 441 (M$^+$−H, 1), 256 (42), 149 (100), 134 (42), 123 (19); Anal. Calcd for C$_{24}$H$_{30}$N$_2$O$_4$S: C, 65.13; H, 6.83; N, 6.33; S, 7.24. Found: C, 64.95; H, 7.00; N, 6.38; S, 7.38.

4.1.16. (3a*R*,4*S*,9b*S*)-8-Methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*c*]quinoline-4-carboxylic acid 1-ethoxycarbonyl-ethyl ester (21). Following the same procedure as reported for **15** using **12** (2.14 g, 6.77 mmol), *p*-anisidine (1.73 g, 14.0 mmol) and cyclopentene (1.53 mL, 17.4 mmol), **21** was afforded as a yellow oil (1.8 g, 38% from **12**). **21**: IR (CH$_2$Cl$_2$, cm^{-1}) 3397, 1755, 1728, 1096, 1042; ^{1}H NMR (200 MHz) δ 6.68–6.46 (m, 3H), 5.15 (1H, q, J=7.2 Hz), 4.40 (1H, br s), 4.19 (2H, q, J=7.2 Hz), 4.02 (1H, d, J=3.2 Hz), 3.69 (3H, s), 3.39 (1H, dt, J=3.2 and 7.3 Hz), 2.99–2.76 (2H, m), 2.21–1.96 (2H, m), 1.92–1.68 (2H, m) 1.51 (3H, d, J=7.2 Hz), 1.26 (3H, t, J=7.2 Hz); ^{13}C NMR (50.2 MHz) δ 171.8, 170.2, 152.8, 137.3, 127.6, 115.8, 113.7, 112.2, 68.9, 61.3, 56.1, 55.4, 41.3, 40.6, 35.3, 24.7, 24.0, 16.8, 13.9; MS (GC) m/z (rel. intensity) 347 (M$^+$, 35), 203 (32), 202 (100), 161 (14), 160 (20); Anal. Calcd for C$_{19}$H$_{25}$NO$_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.66; H, 7.13; N, 4.19.

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