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Revisiting the sparteine surrogate: development of a resolution route to the (–)-sparteine surrogate†

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The improved performance of the sparteine surrogate compared to sparteine in a range of applications has highlighted the need to develop an approach to the (–)-sparteine surrogate, previously inaccesible in gram-quantities. A multi-gram scale, chromatography-free synthesis of the racemic sparteine surrogate and its resolution *via* diastereomeric salt formation with (–)-*O,O'*-di-*p*-toluoyl-L-tartaric acid is reported. Resolution on a 10.0 mmol scale gave the diastereomeric salts in 33% yield from which (–)-sparteine surrogate of 93:7 er was generated. This work solves a key limitation: either enantiomer of the sparteine surrogate can now be readily accessed.

Introduction

In 2002, our group reported the preparation and preliminary synthetic applications of diamine (+)-**1** (Figure 1).[1] We christened diamine (+)-**1** as the "(+)-sparteine surrogate" due to its ability to deliver products in a range of asymmetric reactions with the opposite configuration to those obtained using (–)-sparteine (–)-**2**.[2] Examples include lithiation α to nitrogen,[1,3-7] oxygen[1,8-10] and phosphorus,[11,12] benzylic lithiation-trapping,[8,13] Pd(II)-mediated alcohol oxidation,[1,8] Cu(II)-mediated resolution of racemic BINOL and VAPOL,[8,14] ortholithiation[15] and carbolithiation.[8,16] In terms of synthetic applications, the (+)-sparteine surrogate (+)-**1** has been utilised in a range of natural product syntheses including (–)-kainic acid,[17,18] (–)-amurensinine,[19] (–)-swainsonine,[20] (–)-decarestrictine D,[21] (*S*)-nicotine,[22] (+)-sclerotiorin,[23] (+)-erogorgiaene,[24] (+)-giganin[25] and (–)-hygroline.[26] In each case, (+)-**1** was required to deliver the naturally occurring configuration. Most recently, (+)-**1** has been explored in a route to a key intermediate in the large-scale synthesis of Telaprevir, developed for the treatment of hepatitis C by Vertex Pharmaceuticals and Johnson & Johnson.[27]

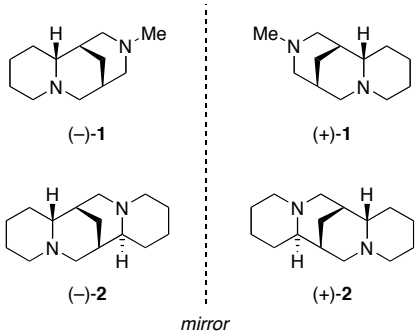
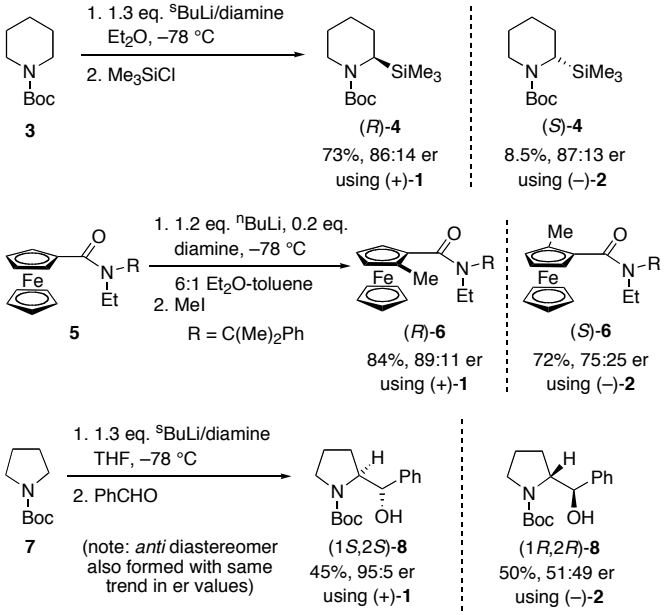


Figure 1. Sparteine surrogate 1 and sparteine 2.

Clearly, (+)-sparteine surrogate's synthetic utility is that it delivers the opposite sense of induction to (–)-sparteine. However, over the last 12 years, two reasons to justify the development of a simple synthetic route to *each* enantiomer of the sparteine surrogate, (+)-**1** and (–)-**1**, have become apparent. First, the commercial availability of (–)-sparteine (–)-**2** has varied considerably over the last few years. Despite the fact that (–)-sparteine *and* (+)-sparteine are natural products,[28] it is only (–)-sparteine that has historically been commercially available. However, since 2010, (–)-sparteine has become much less available and at times completely unavailable from commercial vendors. Perhaps surprisingly, during this time, (+)-sparteine has become commercially available. The reasons for these changes to the supply of sparteine are currently unknown. Second, through detailed investigations comparing (–)-sparteine (–)-**2** with the (+)-sparteine surrogate (+)-**1** in organolithium reactions, we have discovered a number of situations where the (+)-sparteine surrogate (+)-**1** gives superior results to (–)-sparteine (–)-**2** (selected examples in Scheme 1).



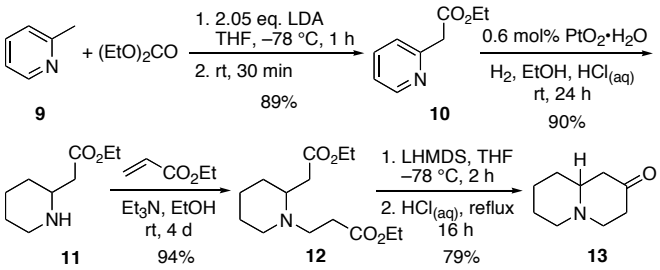
Scheme 1

Significantly, we have found that the *s*-BuLi/(+)-**1** complex is more reactive than *s*-BuLi/(–)-**2** in the lithiation α to nitrogen and oxygen[29,30] (even though (+)-sparteine surrogate (+)-**1** was designed using the 3-D structure of (–)-sparteine (–)-**2** as a guide). This means that, for some substrates, higher yields of product from lithiation-trappings can be obtained with *s*-BuLi/(+)-**1** than with *s*-BuLi/(–)-**2**, as illustrated by the conversion of *N*-Boc piperidine **3** into silylated piperidine **4** (Scheme 1).[31,32] The difference in reactivity between organolithium/(+)-**1** and organolithium/(–)-**2** complexes also manifests itself in improved enantioselectivity with (+)-**1** in two-ligand[29,30,33] and one-ligand[34,35] catalytic asymmetric deprotonations (*e.g.* conversion of ferrocene amide **5** into **6**, Scheme 1). Finally, using ^{1}H and ^{6}Li NMR spectroscopy, we have demonstrated that diamine (+)-**1** is a better coordinator to *i*-PrLi than (–)-**2** in THF.[36] As a result, the first examples of asymmetric deprotonation using *s*-BuLi/chiral diamine in THF were reported: transformation of *N*-Boc pyrrolidine **7** into (1*S*,2*S*)-**8** or (1*R*,2*R*)-**8** (Scheme 1).

Due to the highlighted differences between the sparteine surrogate **1** and sparteine **2** coupled with the variability in the supply of sparteine, ready access to each enantiomer of the sparteine surrogate (+)-**1** and (–)-**1** is now required. Diamine **1** is readily accessible as its (+)-antipode since it is synthesised from naturally occurring (–)-cytisine which possesses the requisite absolute stereochemistry.[1,37] However, (+)-cytisine[38,39] and the (–)-sparteine surrogate (–)-**1**[3,40-43] are more difficult to synthesise. In 2001, we reported an inefficient resolution of *rac*-**1** *via* inclusion complex formation with a chiral acetylinic alcohol: diamine (–)-**1** was isolated in only 80:20 er and low yield (23%).[3,40] Subsequently, Lesma *et al.* developed two asymmetric syntheses,[41,42] which delivered enantiopure (–)-**1** and (+)-**1** *via* routes which are too long to be of practical value. The shortest route to (–)-**1** (eight steps from commercialy available starting materials) was reported by our group in 2007.[43] However, difficult chromatography at two points renders this route impractical for delivering multi-gram quantities of the (–)-sparteine surrogate (–)-**1**.
Ideally, any route to the sparteine surrogate should enable either enantiomer to be readily generated. With this in mind, the synthesis of *rac*-**1** and resolution would represent the most useful approach. Herein, we report a gram-scale synthesis of *rac*-**1** and a detailed study on the resolution of *rac*-**1**. Our efforts culminated in the development of an efficient resolution procedure, allowing access to the (–)-sparteine surrogate (–)-**1**.

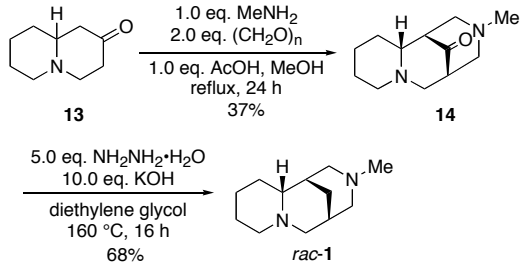
Results and Discussion

Based on an approach described by Scheiber and Nemes,[44] the synthesis of sparteine surrogate *rac*-**1** starting from ethyl 2-pyridyl acetate **10** has previously been reported by our group.[40] A key intermediate in this approach is bicyclic amino ketone **13** and our new, optimised, gram-scale synthesis of amino ketone **13** is outlined in Scheme 2. Due to the relative high cost of ethyl 2-pyridyl acetate **10**, we started the synthesis by preparing **10** from 2-picoline **9** using a method devised from literature precedent.[45] Thus, a mixture of 2-picoline **9** and diethyl carbonate was treated with 2.05 equiv. of LDA in THF at –78 °C. Lithiation and subsequent acylation gave an 89% yield of pyridinyl ester **10** after purification by distillation: 14.7 g of **10** was produced from 9.3 g of **9**. Next, pyridine hydrogenation was carried out using platinum(IV) oxide and hydrogen under acidic conditions. Notably, we were able to reduce the platinum loading from 3 mol% to 0.6 mol% without a detrimental effect on the efficiency and yield: 25.0 g of **10** delivered 23.3 g of **11** (90% yield) which was pure enough to be used directly in the next step. The reaction of **11** (21.0 g) with ethyl acrylate, albeit proceeding slowly (4 days), gave bis amino ester **12** (31.3 g) in 94% yield after distillation. Finally, Dieckmann cyclisation of **12** (16.0 g) using LHMDS and acid-mediated hydrolysis-decarboxylation gave 7.15 g of amino ketone **13** (79% yield), which was sufficiently pure for use in the next step.



Scheme 2

The conversion of amino ketone **13** into sparteine surrogate *rac*-**1** is summarised in Scheme 3. Unfortunately, the double Mannich reaction of **13** to **14** did not scale-up very effectively. We had previously reported a 58% yield of bispidinone **14** on a 1.0 g (6.6 mmol) scale.[40] In contrast, a 37% yield of **14** was obtained starting from 7.95 g (52.2 mmol) of amino ketone **13**.
In an attempt to identify the reason for the low yield, the reaction was monitored by GC analysis (Figure 2). This revealed that although around half of the starting material was converted into the product in the first 10 minutes of the reaction, it took 24 hours for all of the starting material to be consumed (not shown in Figure 2). The reason for this behaviour is not understood. In the end, we concluded that the low yield was mainly due to problems with the purification of bispidinone **14**[46] and a 37% yield of bispidinone **14** was our best result on a multi-gram scale. Wolff-Kishner reduction of bispidinone **14** to give sparteine surrogate *rac*-**1** proceeded uneventfully (68% yield; 4.1 g of **14** gave 2.6 g of **1**). With quantities of sparteine surrogate *rac*-**1** in hand, a chiral stationary phase (CSP)-GC analytical method was developed for separating its enantiomers. Optimum separation was achieved using a Cyclodex B column at 110-140 °C (ramp rate of 1 °C min^{-1}).



Scheme 3

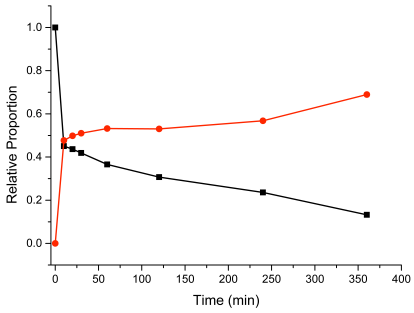
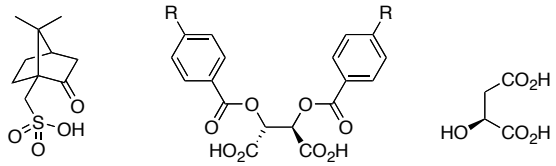


Figure 2. GC monitoring of the double Mannich reaction of 13 (black line) to give 14 (red line) over the first 360 min of reaction.

For the study of the classical resolution of sparteine surrogate *rac*-**1**, four representative chiral acids were chosen: (+)-camphorsulfonic acid (+)-**15**, two tartaric acid derivatives (–)-**16** and (–)-**17** and (–)-malic acid (–)-**18** (Figure 3). An initial solvent screen was carried out in acetone, acetonitrile, *iso*-propanol (IPA) and methyl *tert*-butyl ether (MTBE). The following procedure was adopted for the resolution screening protocol. 19 mg (0.1 mmol) of diamine *rac*-**1** and 0.5 equiv. of the chiral acid were stirred in ~20 μL of solvent at room temperature for 16 h. To collect any solid (diastereomeric salts) that was formed, ~200 μL of solvent was added and the solid was collected by filtration, washing with ~600 μL of solvent. The % yield of the diastereomeric salts (solid) was determined at this point. The solid was then dissolved in 20% $KOH_{(aq)}$ and the resulting diamine **1** was extracted into MTBE. After solvent removal, resolved diamine **1** was analysed by CSP-GC to determine the ratio of (–)-**1**:(+)-**1**. The CSP-GC peaks corresponding to (–)-**1** and (+)-**1** were identified by doping a sample of *rac*-**1** with (+)-**1** which had been synthesised from (–)-cytisine. The results obtained using the four acids and the four solvents are summarised in Table 1.

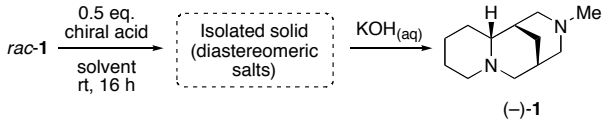


(+)-**15** (–)-**16** (R = H) (–)-**17** (R = Me) (–)-**18**

Figure 3. Chiral acids selected for the resolution studies.

We elected to start with (+)-camphorsulfonic acid (+)-**15** as it had previously been used by Leonard to successfully resolve racemic sparteine **2**.[47] Unfortunately, (+)-**15** was uniformly unsuccessful in resolving *rac*-**1**: solid failed to form in three of the solvents (entries 1-3) and, although solid did form in MTBE, the diamine generated from it was found to be essentially racemic (entry 4). Much better success was noted with the tartaric acid derivatives. With (–)-**16**, solid formed in acetone (29%) and MTBE (38%) (entries 5 and 8 respectively) with diamine (+)-**1** of 73:27 er being generated from the resolution in acetone (entry 5). Use of (–)-**17** was even more promising with solid being generated in three cases (entries 9, 10 and 12). Of note, although the yield was only 12%, diamine

Table 1 Investigation of the resolution of *rac*-**1** using chiral acids (+)-**15** and (–)-**16**-**18**.



(–)-**1**

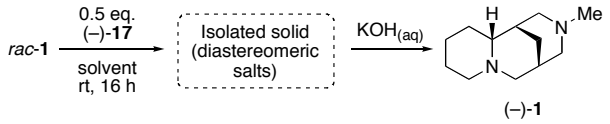
Entry	Acid	Solvent	Yield (%)[a]	Er of **1**, (–):(+)[b]
1	(+)-**15**	acetone	–[c]	n.a.
2	(+)-**15**	MeCN	–[c]	n.a.
3	(+)-**15**	IPA[d]	–[c]	n.a.
4	(+)-**15**	MTBE[e]	43	51:49
5	(–)-**16**	acetone	29	27:73
6	(–)-**16**	MeCN	–[c]	n.a.
7	(–)-**16**	IPA	–[c]	n.a.
8	(–)-**16**	MTBE	38	36:64
9	(–)-**17**	acetone	32	72:28
10	(–)-**17**	MeCN	12	97:3
11	(–)-**17**	IPA	–[c]	n.a.
12	(–)-**17**	MTBE	49	55:45
13	(–)-**18**	acetone	–[c]	n.a.
14	(–)-**18**	MeCN	–[c]	n.a.
15	(–)-**18**	IPA	–[c]	n.a.
16	(–)-**18**	MTBE	–[c]	n.a.

[a] Yield of isolated solid (diastereomeric salts). [b] Er = enantiomer ratio of the free base (–)-**1**:(+)-**1** determined by CSP-GC (see Experimental Section). [c] Solid formation was not observed. [d] IPA = *iso*-propanol. [e] MTBE = methyl *tert*-butyl ether.

(–)-**1** was formed in 97:3 er from the resolution in acetonitrile (entry 10). With (–)-**17**, we also investigated use of 1.0 equiv. of (–)-**17** in acetone for the resolution of *rac*-**1**: this gave a 69% yield of a solid but diamine **1** generated from these was shown to be racemic. Finally, use of malic acid (–)-**18** led to no solid being formed in any of the solvents (entries 13-16).

The standout result from this initial screen was the use of tartaric acid derivative (–)-**17** in acetonitrile which gave diamine (–)-**1** in 97:3 er. Encouraged by this result (notwithstanding the 12% yield) and by the fact that isolatable solids were formed in three out of the four solvents with (–)-**17**, a wide solvent screen using (–)-**17** as the resolving agent was initiated. The hope was to improve the yield whilst maintaining the high er of generated diamine **1**. The resolutions were carried out in the same way on a small scale (0.1 mmol) and the results are presented in Table 2. For this study, 15 different solvents were evaluated with the solvents comprising esters (entries 1-5), ketones (entries 6/7), ethers (entries 8-11), hydrocarbons (entries 12/13) and nitriles (entries 14/15). In ten of these, solid formation was observed, with yields of the diastereomeric salts ranging from 25% (2-MeTHF; entry 10) to 40% (EtOAc; entry 2 and toluene; entry 12). Unfortunately, however, the enantiomeric ratios of sparteine surrogate (–)-**1** generated from the solids were only modest, ranging from 57:43 er (entry 12) to 80:20 er (entry 2). Thus, although the yields were higher than in acetonitrile (12%; Table 1, entry 10), the ers were not as high as that in acetonitrile (97:3 er). As a result, our attention focused on investigating two co-solvents with acetonitrile (entries 16-20). Use of water as the co-solvent completely surpressed the crystallisation process and no solid formation was seen (entries 16-18). In contrast, use of an acetone co-solvent was more successful (entries 19/20). In 4:1 acetonitrile-acetone, the diastereomeric salts were isolated in 23% yield (maximum yield = 50%) and conversion to the (–)-sparteine surrogate (–)-**1** indicated it was formed in 97:3 er (entry 19).

Table 2 Investigation of the resolution of *rac*-**1** using chiral acid (–)-**17**.

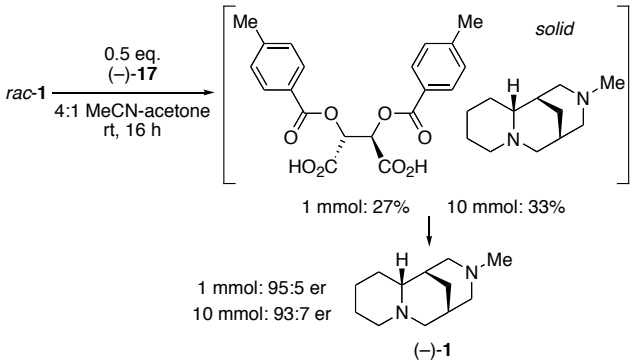


(–)-**1**

Entry	Solvent	Yield (%)[a]	Er of **1**, (–):(+)[b]
1	MeOAc	33	77:23
2	EtOAc	40	80:20
3	*n*-PrOAc	35	77:23
4	*i*-PrOAc	33	69:31
5	*n*-BuOAc	38	66:34
6	MEK[c]	–[d]	n.a.
7	MIBK[e]	–[d]	n.a.
8	Et_2O	25	63:27
9	THF	31	81:19
10	2-MeTHF	25	67:33
11	CPME[f]	28	74:26
12	Toluene	40	57:43
13	Cyclohexane	–[d]	n.a.
14	*n*-BuCN	–[d]	n.a.
15	PhCN	–[d]	n.a.
16	19:1 MeCN-water	–[d]	n.a.
17	9:1 MeCN-water	–[d]	n.a.
18	4:1 MeCN-water	–[d]	n.a.
19	4:1 MeCN-acetone	23	97:3
20	1:1 MeCN-acetone	23	90:10

[a] Yield of isolated solid (diastereomeric salts). [b] Er = enantiomer ratio of the free base (–)-**1**:(+)-**1** determined by CSP-GC (see Experimental Section). [c] MEK methyl ethyl ketone. [d] Solid formation was not observed. [e] MIBK = methyl *iso*-butyl ketone. [f] CPME = cyclopentyl methyl ether

Having identified that the use of (−)-*O,O′*-di-*p*-toluoyl-L-tartaric acid (–)-**17** and a 4:1 acetonitrile-acetone solvent mixture gave the best results for the resolution of sparteine surrogate *rac*-**1**, scale-up of the procedure was investigated. Starting with 1.0 mmol of *rac*-**1** and 0.5 equiv. of (–)-**17** in 0.6 mL of a 4:1 acetonitrile-acetone mixture, a 27% yield of solid diastereomeric salts (characterised by ^{1}H and ^{13}C NMR spectroscopy) was isolated by filtration. Upon base treatment, (–)-sparteine surrogate (–)-**1** was isolated in 95:5 er. From the filtrate, a 67% yield of (+)-sparteine surrogate (+)-**1** of 65:35 er was obtained.



Scheme 4

In a similar way, a 10.0 mmol scale resolution (1.94 g of *rac*-**1**) in 6 mL of solvent delivered the diastereomeric salts in 33% yield from which (–)-**1** of 93:7 er was recovered (Scheme 4). To improve the er further, diamine (–)-**1** of 93:7 er was combined with 0.9 equiv. of (–)-**17** to give a solid (75%) from which diamine (–)-**1** of 95:5 er was generated. Thus, upon scale-up, there was a slight reduction in the er of diamine (–)-**1** that was formed. Nevertheless, these results represent the first gram-scale route to the (–)-sparteine surrogate (–)-**1**. Notably, this synthetic approach is chromatography-free as intermediates/diamine **1** are either not purified or purified by distillation or salt formation.

Conclusions

In conclusion, the resolution route developed in this paper solves a key limitation in sparteine surrogate chemistry: sparteine surrogates (+)-**1** and (–)-**1** can now be readily prepared. Diamine (+)-**1** can be synthesised from (–)-cytisine[1,37] and (–)-**1** can be prepared by resolution of *rac*-**1** (−)-*O,O′*-di-*p*-toluoyl-L-tartaric acid (–)-**17** *via* a chromatography-free route. This is of particular significance as there is a growing list of examples where the sparteine surrogate **1** outperforms sparteine **2**.

Experimental

General

All-non aqueous reactions were carried out under oxygen-free Ar or N_2 using flame-dried glassware. THF was freshly distilled from sodium and benzophenone. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. Brine refers to a saturated solution. Water is distilled water. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Boiling points give for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Chiral stationary phase GC was performed on a Hewlett Packard 6980 series chromatograph.

Procedures and Characterisation Data

Ethyl 2-(pyridin-2-yl)acetate 10. *n*-BuLi (2.5 M solution in hexanes, 84.0 mL, 0.21 mol, 2.05 eq.) was added dropwise to a stirred solution of diisopropylamine (22.3 g, 30.8 mL, 0.22 mol, 2.10 eq.) in THF (100 mL) at –78 °C under Ar. The resulting solution was warmed to 0 °C and stirred at 0 °C for 1 h. Then, the solution was transferred *via* cannula to a stirred solution of 2-picoline **9** (9.3 g, 9.9 mL, 0.10 mol, 1.0 eq.) and diethyl carbonate (35.4 g, 36.3 mL, 0.30 mol, 3.0 eq.) in THF (100 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, the solution was allowed to warm to rt and stirred at rt for 30 min. Saturated $NH_4Cl_{(aq)}$ (50 mL) and water (200 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave ester **10** (14.7 g, 89%) as a bright yellow oil, bp 110-120 °C/2.3 mmHg (lit.,[47] bp 110 °C/3 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (m, 1H, Ar), 7.64 (td, *J* = 7.5, 2.0 Hz, 1H, Ar), 7.28 (d, *J* = 7.5 Hz, 1H, Ar), 7.17 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H, Ar), 4.16 (q, *J* = 7.0 Hz, 2H, C*H*$_2$Me), 3.82 (s, 2H, ArCH_2), 1.24 (t, *J* = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 170.6 (C=O), 154.4 (*ipso*-Ar),

149.4 (Ar), 136.6 (Ar), 123.8 (Ar), 122.0 (Ar), 61.0 (CH$_2$Me), 43.9 (ArCH$_2$), 14.1 (CH$_2$*Me*). Spectroscopic data consistent with those reported in the literature.[48]

Ethyl 2-(piperidin-2-yl)acetate 11. PtO_2•H_2O (223 mg, 0.91 mmol, 0.006 eq.) was added to a stirred solution of pyridine **10** (25.0 g, 151 mmol, 1.0 eq.) in EtOH (250 mL) and 6 M $HCl_{(aq)}$ (45 mL). The reaction flask evacuated under reduced pressure and back filled with N_2 three times. After a final evacuation, H_2 was charged at 2 atm and the reaction mixture was stirred vigorously at rt for 24 h. The mixture was filtered through Celite® and washed with EtOH (300 mL) and the filtrate was evaporated under reduced pressure. Then, the residue was dissolved in 2 M $NH_4OH_{(aq)}$ (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the piperidine **11** (23.2 g, 90%) as a clear oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (q, J = 7.0 Hz, 2H, CH_2Me), 2.96-3.05 (m, 1H, NCH), 2.87 (dddd, J = 10.5, 7.5, 5.5, 2.5 Hz, 1H, NCH), 2.58-2.68 (m, 1H, NCH), 2.33-2.37 (m, 1H, CH_AH$_B$CO$_2$Et), 2.27-2.32 (m, 1H, CH$_A$$H_BCO_2$Et), 2.04 (br s, 1H, NH), 1.68-1.78 (m, 1H, CH), 1.49-1.62 (m, 2H, CH), 1.26-1.44 (m, 2H, CH), 1.22 (t, J = 7.0 Hz, 3H, CH$_2$*Me*), 1.05-1.18 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C=O), 60.3 (CH$_2$Me), 53.3 (NCH), 46.8 (NCH$_2$), 41.7 (CH$_2$), 32.6 (CH$_2$), 26.0 (CH$_2$), 24.6 (CH$_2$), 14.2 (CH$_2$*Me*). Spectroscopic data consistent with those reported in the literature.[49]

Ethyl 3-(2-(2-ethoxy-2-oxoethyl)piperidin-1-yl)propanoate 12. Ethyl acrylate (36.8 g, 40.1 mL, 0.37 mol, 3.0 eq.) was added dropwise to a stirred solution of piperidine **11** (21.0 g, 123 mmol, 1.0 eq.) and Et_3N (74.5 g, 103 mL, 0.74 mol, 6.0 eq.) in EtOH (400 mL) at rt under Ar. The resulting solution was stirred at rt for 4 d. The solvent was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave di-ester **12** (31.3 g, 94%) as a clear oil, bp 155-165 °C/1.0 mmHg (lit.,[3] bp 175-180 °C/1.0 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.0 Hz, 2H, CH_2Me), 4.11 (q, J = 7.0 Hz, 2H, CH_2Me), 2.96–2.82 (m, 2H, NCH), 2.77–2.59 (m, 3H, NCH), 2.45 (t, J = 7.5 Hz, 2H, CH_2CO$_2$Et), 2.39–2.23 (m, 2H, CH_2CO$_2$Et), 1.73–1.30 (m, 6H, CH), 1.24 (t, J = 7.0 Hz, 3H, CH$_2$*Me*), 1.24 (t, J = 7.0 Hz, 3H, CH$_2$*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O), 60.4 (CH$_2$Me), 60.3 (CH$_2$Me), 56.3 (NCH), 50.2 (NCH$_2$), 49.4 (NCH$_2$), 35.7 (CH$_2$), 31.9 (CH$_2$), 30.7 (CH$_2$), 25.2 (CH$_2$), 22.0 (CH$_2$), 14.19 (Me), 14.18 (Me). Spectroscopic data consistent with those reported in the literature.[3]

Hexahydro-1H-quinolizin-2(6H)-one 13. LHMDS (118 mL of a 1 M solution in THF, 118 mmol, 2.0 eq.) was added dropwise to a stirred solution of di-ester **12** (16.0 g, 58.9 mmol, 1.0 eq.) in THF (60 mL) at –78 °C under N_2. After stirring for 2 h at –78 °C, water (40 mL) was added and the solution was warmed to rt. 12 M $HCl_{(aq)}$ (30 mL) was added and the mixture was extracted with MTBE (3 × 100 mL). Then, saturated $K_2CO_{3(aq)}$ was added to the aqueous layer until pH 10 was obtained. The aqueous layer was extracted with MTBE (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude β-keto ester as a yellow oil. Then, 6 M $HCl_{(aq)}$ (300 mL) was added and the resulting solution was stirred and heated at reflux for 16 h. After cooling to rt, the solution was carefully neutralised with solid potassium carbonate until gas evolution stopped and the solution was saturated. The solid was removed by filtration and washed with MTBE (100 mL). Then, the layers of the filtrate were separated and the aqueous was extracted with MTBE (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amino ketone **13** (7.15 g, 79%) as a pale yellow oil which was sufficiently pure by ^{1}H NMR spectroscopy, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11-3.03 (m, 1H, NCH), 3.00-2.92 (m, 1H, NCH), 2.73-2.60 (m, 1H, NCH), 2.39-2.22 (m, 4H, NCH + CH$_2$CO), 2.12-1.98 (m, 2H, CH$_2$CO), 1.80-1.56 (m, 4H, CH), 1.41-1.15 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.4 (C=O), 61.8 (NCH), 55.4 (NCH$_2$), 55.3 (NCH$_2$), 48.1 (CH$_2$CO), 41.3 (CH$_2$CO), 33.6 (CH$_2$), 25.5 (CH$_2$), 23.2 (CH$_2$). Spectroscopic data consistent with those reported in the literature.[50]

3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocin-12-one 14. Methylamine (6.5 mL of a 8.0 M solution in EtOH, 52.2 mmol, 1.0 eq.) was added to a stirred solution of amino ketone **13** (7.95 g, 52.2 mmol, 1.0 eq.), paraformaldehyde (3.14 g, 105 mmol, 2.0 eq.) and acetic acid (3.13 g, 2.99 mL, 52.2 mmol, 1.0 eq.) in MeOH (80 mL) at rt under N_2. The resulting solution was stirred and heated at reflux for 24 h. After cooling to rt, the solvent was evaporated under reduced pressure and 50% $KOH_{(aq)}$ (50 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diazatricyclic ketone **14** (4.07 g, 37%) as a colourless oil, bp 160-170 °C/1.0 mmHg (lit.,[3] bp 140-150 °C/0.8 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (dd, J = 11.0, 3.0 Hz, 1H, NCH or CHCO), 3.09–2.95 (m, 3H, NCH or CHCO), 2.94–2.86 (m, 1H, NCH or CHCO), 2.79 (ddd, J = 11.0, 8.5, 1.5 Hz, 1H, NCH or CHCO), 2.59–2.52 (m, 1H, NCH or CHCO), 2.40 (dd, J = 11.5, 3.0 Hz, 1H, NCH or CHCO), 2.36–2.29 (m, 1H, NCH or CHCO), 2.25 (s, 3H, NMe), 2.12 (dt, J = 11.0, 2.0 Hz, 1H, NCH or CHCO), 1.97–1.86 (m, 1H, NCH or CHCO), 1.81–1.70 (m, 1H, CH), 1.69–1.52 (m, 3H, CH), 1.41–1.32 (m, 1H, CH), 1.29–1.12 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.7 (C=O), 66.8 (NCH), 62.5 (NCH$_2$), 60.5 (NCH$_2$), 56.4 (NCH$_2$), 55.0 (NCH$_2$), 52.2 (NMe), 47.5 (CH), 45.4 (CH), 29.9 (CH$_2$), 25.5 (CH$_2$), 23.4 (CH$_2$). Spectroscopic data consistent with those reported in the literature.[3]

3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine *rac*-1. Hydrazine monohydrate (4.89 g, 4.74 mL, 97.7 mmol, 5.0 eq.) was added to a stirred solution of diazatricyclic ketone **14** (4.07 g, 19.5 mmol, 1.0 eq.) and KOH (11.0 g, 195 mmol, 10 eq.) in diethylene glycol (60 mL) at rt under N_2. The resulting solution was stirred and heated at 160 °C for 16 h. After cooling to 60 °C, H_2O (50 mL) and 1 M $HCl_{(aq)}$ (50 mL) were added. The aqueous layer was extracted with MTBE (3 × 50 mL). Then, the pH of the aqueous layer was adjusted to pH 12 with 50% $KOH_{(aq)}$. The aqueous was extracted with MTBE (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine *rac*-**1** (2.56 g, 68%) as a colourless oil, bp 170-180 °C/2.0 mmHg (lit.,[3] bp 150-160 °C/0.8 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00-2.95 (m, 2H, NCH), 2.89 (m, 2H, NCH), 2.22 (ddd, J = 11.0, 3.5, 1.5 Hz, 1H, NCH), 2.14-2.11 (m, 1H, NCH), 2.13 (s, 3H, NMe), 1.94 (dd, J = 11.5, 3.0 Hz, 1H, NCH), 1.87 (br d, J = 11.0 Hz, 1H, NCH), 1.77-

1.46 (m, 9H, NCH + CH), 1.32-1.20 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 66.4 (NCH), 60.4 (NCH_2), 60.3 (NCH_2), 57.6 (NCH_2), 56.3 (NCH_2), 47.2 (NMe), 35.0 (CH), 33.8 (CH_2), 30.4 (CH), 25.5 (CH_2), 24.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[3]

General procedure for resolution of sparteine surrogate *rac*-1. A solution of resolving agent (0.05 mmol, 0.5 eq.) in the minimum amount of solvent was added to a stirred solution of *rac*-**1** (19 mg, 0.10 mmol, 1.0 eq.) in solvent (20 µL) at rt. The resulting mixtures were stirred at rt for 16 h. Solvent (0.2 mL) was added, crystals (if formed) were filtered, washed with solvent (0.6 mL) and dried under reduced pressure. Then, the crystals were dissolved in 20% $KOH_{(aq)}$ (3 mL) and MTBE (2 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 2 mL). The combined organics were dried by passing through a PTFE membrane under gravity and evaporated under reduced pressure to give resolved surrogate **1**. The er of **1** was determined by CSP-GC using cyclodex-B column (110-140 °C, 1 °C/min), (+)-**1** 22.8 min, (–)-**1** 23.1 min.

(1*S*,5*R*,11a*R*)-3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine (–)-1. Using the general procedure, (+)-camphor-10-sulfonic acid (+)-**15** (12 mg, 0.05 mmol, 0.5 eq.) in MTBE (300 µL) and *rac*-**1** (19 mg, 0.10 mmol, 1.0 eq.) in MTBE (20 µL) gave salt (+)-**15**.(–)-**1** (10 mg, 43%) as a white solid, mp 89-91 °C; IR (ATR) 3477, 3067, 2923, 2771, 1736 (C=O), 1511, 1466, 1404, 1351, 1328, 1321, 1301, 1288, 1264, 1224, 1170 (S=O), 1131, 1107, 1040, 716, 614 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 3.41 (dd, J = 12.0, 1.5 Hz, 1H, NCH), 3.33-3.24 (m, 4H, NCH + CH), 3.22-3.15 (m, 1H, NCH), 2.98-2.86 (m, 2H, NCH), 2.76 (d, J = 15.0 Hz, 1H, CH) 2.74-2.64 (m, 2H, NCH + CH), 2.63-2.58 (m 1H, NCH), 2.47 (s, 3H, NMe), 2.47-2.42 (m, 1H, NCH), 2.38-2.30 (m, 1H, CH), 2.14 (br s, 1H, CH), 2.18-2.09 (m, 2H, CH), 1.94-1.85 (m, 4H, CH + CH), 1.85-1.66 (m, 4H, CH), 1.65-1.47 (m, 2H, CH + CH), 1.47-1.37 (m, 1H, CH), 1.14 (s, 3H, Me), 0.86 (s, 3H, Me); ^{13}C NMR (100.6 MHz, CD_3OD) δ 218.2 (C=O), 67.7 (NCH), 61.1 (NCH_2), 61.0 (NCH_2), 59.6 (*C*C=O), 57.2 (NCH_2), 57.0 (NCH_2), 48.1 (CH_2SO_3H), 45.5 (NMe), 44.1 (CH), 43.6 (CH_2), 34.2 (CH), 32.3 (CH_2), 30.2 (CH_2), 29.9 (CH), 27.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 24.2 (CH_2), 20.5 (Me), 20.1 (Me), quaternary carbon not resolved; MS (ESI) *m/z* 195 (M + H)$^+$; HRMS *m/z* calcd for $C_{12}H_{22}N_2$ (M + H)$^+$ 195.1856, found 195.1862 (–3.1 ppm error); MS (ESI) *m/z* 231 (M – H)$^–$; HRMS *m/z* calcd for $C_{10}H_{16}O_4S$ (M – H)$^–$ 231.0697, found 231.0697 (–0.7 ppm error) and then the resolved surrogate (–)-**1** (51:49 er by CSP-GC), CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**1** 22.9 min, (–)-**1** 23.3 min.

(1*S*,5*R*,11a*R*)-3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine (+)-1. Using the general procedure, (−)-*O,O′*-dibenzoyl-L-tartaric acid (–)-**16** (18 mg, 0.05 mmol, 0.5 eq.) in MTBE (100 µL) and *rac*-**1** (19 mg, 0.10 mmol, 1.0 eq.) in MTBE (20 µL) gave salt [(–)-**16**]$_2$.(+)-**1** (7 mg, 38%) as a white solid, mp 133-135 °C (dec.); IR (ATR) 3061, 2933, 2859, 2771, 1713 (C=O), 1608, 1582, 1462, 1463, 1359, 1332, 1270, 1262, 1191, 1126, 1107, 1065, 1027, 1003, 990, 892, 850, 780, 714 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 8.19-8.17 (m, 2H, Ph), 7.63-7.53 (m, 1H, Ph), 7.48-7.44 (m, 2H, Ph), 5.90 (s, 1H, C*H*CO_2H), 3.38 (br d, J = 12.0 Hz, 1H, NCH), 3.26 (br d, J = 12.0 Hz, 2H, NCH), 3.20-3.12 (m, 1H, NCH), 2.93-2.83 (m, 2H, NCH), 2.68 (dt, J = 11.5, 2.5 Hz, 1H, NCH), 2.58 (br d, J = 12.0 Hz, 1H, NCH), 2.45 (s, 3H, NMe), 2.40 (ddd, J = 12.0, 4.0, 2.0 Hz, 1H, NCH), 2.11 (br s, 1H, CH), 1.92-1.81 (m, 4H, CH + CH), 1.75-1.67 (m, 4H, CH), 1.58-1.44 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CD_3OD) δ 173.4 (C=O), 167.9 (C=O), 133.8 (Ph), 132.2 (*ipso*-Ph), 131.1 (Ph), 129.2 (Ph), 77.0 (*C*HCO_2H), 67.7 (NCH), 61.1 (NCH_2), 61.0 (NCH_2), 57.2 (NCH_2), 57.0 (NCH_2), 45.5 (NMe), 34.2 (CH), 32.3 (CH_2), 30.2 (CH_2), 29.9 (CH), 25.6 (CH_2), 24.2 (CH_2); MS (ESI) *m/z* 195 (M + H)$^+$; HRMS *m/z* calcd for $C_{12}H_{22}N_2$ (M + H)$^+$ 195.1856, found 195.1852 (+1.8 ppm error); MS (ESI) *m/z* 357 (M – H)$^–$; HRMS *m/z* calcd for $C_{18}H_{14}O_8$ (M – H)$^–$ 357.0616, found 357.0625 (–3.1 ppm error) and then the resolved surrogate (–)-**1** (64:36 er by CSP-GC), CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**1** 22.9 min, (–)-**1** 23.3 min.

(1*S*,5*R*,11a*R*)-3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine (–)-1. A solution of (−)-*O,O′*-di-*p*-toluoyl-L-tartaric acid (–)-**17** (193 mg, 0.5 mmol, 0.5 eq.) in 4:1 MeCN-acetone (0.3 mL) was added to a stirred solution of *rac*-**1** (194 mg, 1.0 mmol, 1.0 eq.) in 4:1 MeCN-acetone (0.3 mL) at rt. The resulting mixture was stirred at rt for 16 h. The solid was collected by filtration, washed with cold 4:1 MeCN-acetone (2 mL) and dried under reduced pressure to give salt (–)-**17**.(–)-**1** (154 mg, 27%) as a white solid, mp 155-156 °C (dec.); IR (ATR) 2924, 2776, 1718 (C=O, ester), 1612, 1510, 1466, 1324, 1290, 1254, 1210, 1178, 1155, 1124, 1108, 1072. 1062, 1020, 988, 916, 899, 840, 749, 686 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (d, J = 8.0 Hz, 4H, Ar), 7.29 (d, J = 8.0 Hz, 4H, Ar), 5.87 (s, 2H, C*H*CO_2H), 3.39 (br d, J = 12.0 Hz, 1H, NCH), 3.29-3.21 (m, 2H, NCH), 3.20-3.12 (m, 1H, NCH), 2.95-2.82 (m, 2H, NCH), 2.69 (dt, J = 11.5, 2.5 Hz, 1H, NCH), 2.62-2.55 (m, 1H, NCH), 2.46 (s, 3H, NMe), 2.49-2.38 (m, 1H, NCH), 2.41 (s, 6H, Ar*Me*), 2.17-2.10 (m, 1H, CH), 1.91-1.83 (m, 4H, CH + CH), 1.84- 1.64 (m, 4H, CH), 1.58-1.44 (m, 1H, CH); ^{13}C NMR (100.6 MHz, CD_3OD) δ 171.9 (C=O), 169.5 (C=O), 145.3 (*ipso*-Ar), 131.1 (Ar), 130.0 (Ar), 128.6 (*ipso*-Ar), 75.2 (*C*HCO_2H), 67.7 (NCH), 61.1 (NCH_2), 61.0 (NCH_2), 57.2 (NCH_2), 56.9 (NCH_2), 45.5 (NMe), 34.2 (CH), 32.2 (CH_2), 30.2 (CH_2), 29.9 (CH), 25.5 (CH_2), 24.2 (CH_2), 21.7 (Ar*Me*); MS (ESI) *m/z* 195 (M + H)$^+$; HRMS *m/z* calcd for $C_{12}H_{22}N_2$ (M + H)$^+$ 195.1856, found 195.1864 (–4.0 ppm error); MS (ESI) *m/z* 385 (M – H)$^–$; HRMS *m/z* calcd for $C_{20}H_{18}O_{10}$ (M – H)$^–$ 385.0929, found 385.0947 (–3.9 ppm error). The filtrate was evaporated under reduced pressure and Et_2O (5 mL) and 2 M $NaOH_{(aq)}$ (5 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the surrogate (+)-**1** (131 mg, 67%, 65:35 er by ^{1}H NMR spectroscopy in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol[37]) as a pale yellow oil. Then, a portion of salt (–)-**17**.(–)-**1** (20 mg, 0.034 mmol) was dissolved in 20% $KOH_{(aq)}$ (2 mL) and MTBE (2 mL). The layers were separated and the aqueous layer was extracted with MTBE (2 × 2 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the resolved surrogate (–)-**1** (95:5 er by CSP-GC), CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**1** 23.1 min, (–)-**1** 23.2 min.

(1*S*,5*R*,11a*R*)-3-Methyldecahydro-1H-1,5-methanopyrido[1,2-*a*][1,5]diazocine (–)-1. A solution of (−)-*O,O′*-di-*p*-toluoyl-L-tartaric acid (–)-**17** (1.93 g, 5.0 mmol, 0.5 eq.) in 4:1 MeCN-acetone (2 mL) was added to a stirred solution of *rac*-**1** (1.94 g, 10 mmol, 1.0 eq.) in 4:1 MeCN-acetone (4 mL) at rt. The resulting mixture was stirred at rt for

16 h. The solid was collected by filtration, washed with cold 4:1 MeCN-acetone (5 mL) and dried under reduced pressure to give salt (–)-**17**.(–)-**1** (1.92 g, 33%) as a white solid. Then, a portion of the salt (1.82 g, 3.13 mmol) was dissolved in 20% $KOH_{(aq)}$ (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the resolved surrogate (–)-**1** (606 mg, 99%, 93:7 er by CSP-GC), CSP-GC: Cyclodex-B column (110-140 °C, 1 °C/min), (+)-**1** 23.0 min, (–)-**1** 23.3 min.
Then, a solution of (−)-*O,O′*-di-*p*-toluoyl-L-tartaric acid (–)-**17** (1.12 g, 2.91 mmol, 0.93 eq.) in 4:1 MeCN-acetone (2 mL) was added to a stirred solution of surrogate (–)-**1** (606 mg, 3.12 mmol, 1.0 eq., 93:7 er) in 4:1 MeCN-acetone (4 mL) at rt. The resulting mixture was stirred at rt for 5 h. The solid was collected by filtration, washed with cold 4:1 MeCN-acetone (5 mL) and dried under reduced pressure to give salt (–)-**17**.(–)-**1** (1.36 g, 75%) as a white solid. Then, a portion of salt (–)-**17**.(–)-**1** (200 mg, 0.34 mmol) was dissolved in 2 M $NaOH_{(aq)}$ (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the resolved surrogate (–)-**1** (67 mg, 100%, 95:5 er by ^{1}H NMR spectroscopy in the presence of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol[37]) as a pale yellow oil, $[\alpha]_D$ –25.5 (*c* 1.0 in EtOH) (lit.,[3] $[\alpha]_D$ +26.5 (*c* 1.0 in EtOH for (+)-**1**).

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Notes and references

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