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Concise access to indolizidine and pyrroloazepine skeleta *via* intramolecular Schmidt reactions of azido 1,3-diketones†

Duanpen Lertpibulpanya[a] and Stephen P. Marsden*[b]

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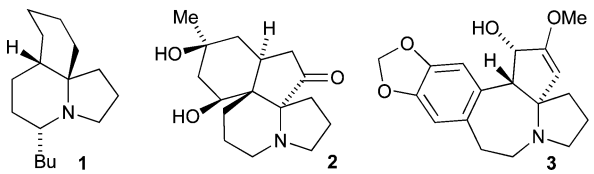
Readily prepared 2-alkyl-2-azidopropylcycloalkyl-1,3-diones undergo intramolecular Schmidt rearrangement with a range of hard Lewis acids, leading to indolizidinediones and pyrroloazepinediones. Chiral aluminium-based Lewis acids could also be used to mediate this symmetry-breaking transformation, but no significant asymmetric induction was observed.

Introduction

Indolizidine alkaloids containing quaternary asymmetric centres at the carbon ring-fusion position are widely distributed in nature, exemplified by structures such as lepadiformine C **1**[1] and the *Lycopodium* alkaloid serratine **2**.[2] Compounds containing the homologous pyrroloazepine skeleton are also known, with perhaps the most important examples being esters of cephalotaxine **3**,[3] which show efficacy as anti-leukaemic agents.[4]



The traditional Schmidt reaction involves insertion of hydrazoic acid into a C–H or C–C bond adjacent to an aldehyde or ketone carbonyl group, leading to amide formation and loss of dinitrogen.[5] Attempts to use alkyl azides in the reaction (leading to substituted amides) have met with mixed results. Intermolecular reactions of simple alkyl azides are known but are not reliably successful.[6] Aubé *et al.* have, however, pioneered intramolecular variants of the reaction with great success,[7,8] leading to applications in the total synthesis of the alkaloidal natural products indolizidine 209B,[9] aspidospermine,[10] sparteine,[11] dendrobatid alkaloid 251F[12] and stenine,[13] as well as the homoerythrina alkaloid skeleton.[14]

As part of our interest in the desymmetrisation of prochiral azidodiketones of general structure **4**,[15] we considered that facile entry to the above ring systems would be achieved by way of an intramolecular Schmidt reaction of the alkyl azide with one of the ketones; usefully the two carbonyl groups in the ketoamide product would be distinguishable in subsequent chemoselective reactions, facilitating further elaboration of the basic skeleton and paving the way for applications in target synthesis. The potential for enantioselective variants of the reaction utilising chiral Lewis acids to discriminate between the prochiral ketones was also a key consideration.

A generalised summary of the proposed chemistry is shown in Fig. 1. Lewis acid activation of one of the ketones of **4** initiates nucleophilic attack by the pendant azide. Rearrangement of the resulting intermediate **5** can potentially occur to yield the desired fused bicyclic product **6** (path a), or the bridged bicyclic amide **7** (path b). All available literature precedent supports the exclusive formation of **6** (either due to conformational requirements, or due to the instability of the bridged amide in **7**[8]), but this remained to be verified in the current system. In particular, we had concerns that the presence of the inductively-withdrawing acyl substituent on the migrating carbon in path a might disfavour this pathway, leading either to the competing reaction through path b, or the shutdown of the Schmidt pathway altogether. At the outset of this work, there was only a single example of the intramolecular Schmidt reaction of an azidopropyl-substituted 1,3-diketone, promoted by a Brønsted acid (trifluoroacetic acid).[8] We therefore needed to demonstrate that the reactions could be promoted effectively by Lewis acids (and in particular by Lewis acids amenable to substitution with chiral ligands) as well as defining more clearly the scope of the reaction. We report herein the results of these studies.

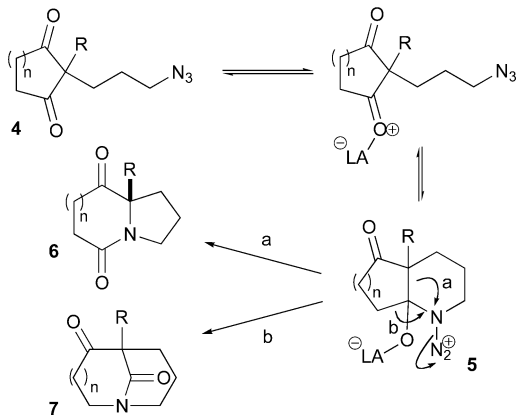


Fig. 1 Potential pathways in the intramolecular Schmidt reaction of **4**.

[a]*Department of Chemistry, Imperial College, London, UK SW7 2AY*
[b]*School of Chemistry, University of Leeds, Leeds, UK LS2 9JT. E-mail: s.p.marsden@leeds.ac.uk; Fax: 44 113 343 6565; Tel: 44 113 343 6425*

† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR for compounds **4a–c**, **6a–c** and **10/11a–c**. See DOI: 10.1039/b608801e

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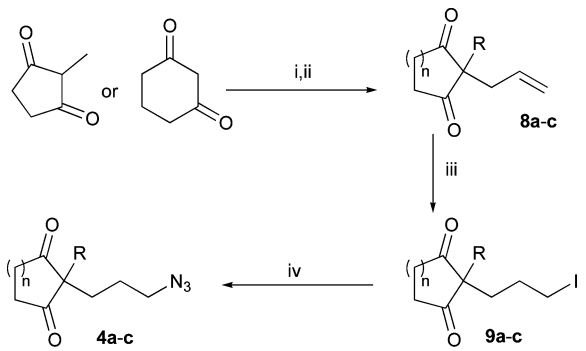
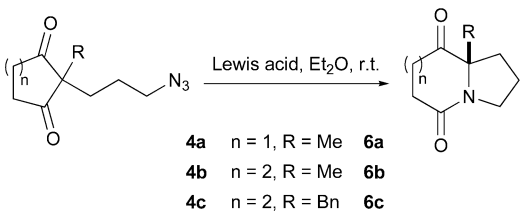
Results and discussion

The requisite azidodiketones **4a–c** were prepared from 2-methylcyclopentane-1,3-dione and cyclohexane-1,3-dione as shown in Scheme 1. Hydroboration of the 2-alkyl-2-allyl diketones **8a–c**[16,17] was carried out with an iodinative work-up according to the general method of Kabalka *et al.*[18] to give primary iodides **9a–c**. Nucleophilic displacement of the iodide with sodium azide in aqueous acetone gave the desired azidodiketones **4a–c**. The azides could be readily prepared in this manner on a multi-gram scale (**caution**: although we have not experienced any problems with these materials, all preparations, purifications and reactions of the azides were carried out behind a blast shield with appropriate precautions).[19]



Scheme 1 *Reagents, conditions and yields*: (i) 5 M NaOH, MeI or BnBr, 65 °C or 100 °C respectively; (ii) 1 N NaOH, 1% Bu_4NI, allyl bromide, r.t. (**8a** 84%, step 2 only; **8b** 52% and **8c** 43% over 2 steps); (iii) 1.2 eq. $BH_3{\cdot}Me_2S$, 2.5 eq. cyclohexene, THF, 0 °C then **8a–c**, 0 °C to r.t., then NaOAc–MeOH, I_2, r.t. (**9a** 35%, **9b** 55%, **9c** 42%); (iv) NaN_3, 1% Bu_4NI, acetone–H_2O, r.t. (**4a** 85%, **4b** 87%, **4c** 79%).

With the substrates in hand, attention then turned to an investigation of the Schmidt reaction promoted by various Lewis acids. The results of our screening are summarised in Scheme 2 and Table 1. The hard Lewis acids boron trifluoride and titanium(IV) chloride had previously been shown to be effective promoters of the intramolecular Schmidt reactions of azidoketones, and we were pleased to find that these reagents were also effective in the current programme, giving good yields of the rearranged bicyclic products **6a** and **6b**. No trace of the bridged lactams **7** was observed in any of the reactions. Super-stoichiometric Lewis acid was required for the reaction to proceed at an acceptable rate, likely because of sequestration of the first equivalent of reagent by the strongly Lewis-basic lactam in products **6**. Ethylaluminium dichloride was also found to be an excellent reagent for the transformation. We next attempted to utilise Lewis acids which might be amenable



Scheme 2 Schmidt rearrangement of diketoazides **4a–c**.

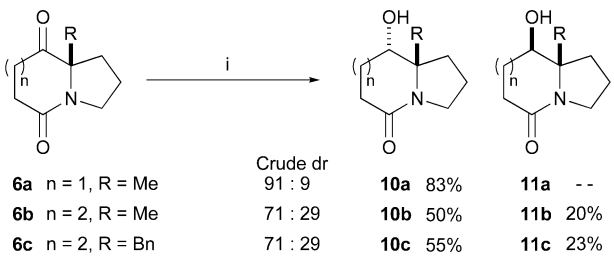
Table 1 Schmidt rearrangement of diketoazides **4a–c** by Lewis acids

Entry	Azide	Lewis acid (eq.)	Time/h	Product	Yield
1	**4a**	$BF_3{\cdot}OEt_2$ (4)	24	**6a**	65%
2	**4a**	$TiCl_4$ (2.5)	1	**6a**	89%
3	**4a**	$EtAlCl_2$ (2.5)	6	**6a**	83%
4	**4a**	$Cu(OTf)_2$ (2.5)[a]	72	**6a**	n. r.
5	**4a**	$ZnCl_2$ (2.5)	72	**6a**	n. r.
6	**4a**	$Yb(OTf)_3$[a]	72	**6a**	n. r.
7	**4b**	$BF_3{\cdot}OEt_2$ (2.5)	24	**6b**	52%[b]
8	**4b**	$BF_3{\cdot}OEt_2$ (4)	24	**6b**	85%
9	**4b**	$TiCl_4$ (1.1)	1	**6b**	67%
10	**4b**	$EtAlCl_2$ (1.1)	24	**6b**	60%
11	**4b**	$EtAlCl_2$ (2.5)	6	**6b**	80%
12	**4c**	$EtAlCl_2$ (2.5)	24	**6c**	87%

[a] THF used as solvent in place of Et_2O. [b] Starting material (20%) also recovered.

to use with external chiral ligands; disappointingly, the use of copper(II) triflate, zinc chloride and ytterbium(III) triflate all returned clean starting material (>90% recovery in all cases) after 72 hours. The failure of zinc chloride to promote the reaction was particularly disappointing given that this reagent had successfully been used in intramolecular Schmidt reactions of azidoaldehydes,[8] giving an indication of the demanding nature of the present transformations.

Although disappointed by the lack of scope of potential Lewis acids, we were encouraged by the clean nature of the reactions and aware of the potential for chiral Lewis acids based upon titanium, boron and aluminium. Before embarking on screens for enantioselective variants, we needed to identify an assay for enantiomeric purity. The lack of a potent chromophore in products **6a–c** coupled with their likely low volatility prompted us to consider non-chromatographic options. In the event, chemoselective sodium borohydride reduction of the ketoamides gave a mixture of diastereomeric alcohols **10**/**11a–c** (Scheme 3). The identity of the diastereomers was not unambiguously established but is tentatively assigned as shown based upon the literature precedent for stereoselective reductions in the corresponding carbocyclic series.[20] Chromatographic separation of the diastereomers and derivatisation of the major diastereomers as their Mosher's esters allowed resolution of the antipodal alcohols by ^1H or ^{19}F NMR.



Scheme 3 *Reagents and conditions*: (i) $NaBH_4$, MeOH, r.t.

We then commenced screening of chiral Lewis acids. Initial attempts focused on boron and titanium-based Lewis acids, in the form of Corey's *N*-tosyl-L-tryptophan-derived oxazaborolidine[21] and Mikami *et al.*'s (*S*)-BINOLTiCl_2 respectively.[22] After 72 hours at room temperature, only starting material was observed. However, more encouraging results were obtained with chiral aluminium-based Lewis acids, namely L-menthyloxyaluminium

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Table 2 Attempted asymmetric Schmidt rearrangements

Entry	Azide	Lewis acid	Product	Conv. (%)[a]	Yield (%)[b]	ee (%)[c]
1	**4a**	**12**	**5a**	40	35	0
2	**4a**	**13**	**5a**	22	18	6
3	**4b**	**12**	**5b**	67	50	5
4	**4b**	**13**	**5b**	50	25	4
5	**4c**	**12**	**5c**	40	27	0
6	**4c**	**13**	**5c**	14	10	0

[a] Conversion measured from crude ^{1}H NMR spectrum. [b] Isolated yield. [c] Determined by ketone reduction and Mosher's ester derivatisation.

dichloride **12** and (*S*)-BINOLAlCl **13**. These reagents proved competent enough Lewis acids to promote the reaction, although as seen in Table 2, the conversions after 72 hours were far from complete. In three cases, a small optical rotation was observed for the products but on derivatisation by reduction–esterification to the Mosher's derivative as outlined above, asymmetric induction was found to be less than 10% in all cases.

Conclusions

Prochiral 2-(3-azidopropyl)-1,3-diketones, readily prepared from commercial cycloalkyldiones, undergo completely regioselective Schmidt rearrangement yielding desymmetrised racemic bicyclic ketoamides. Attempts at asymmetric variants of the reaction resulted in modest conversions to product with aluminium-based Lewis acids, but with negligible asymmetric induction. Future exploration of this process will require the identification of more active catalyst systems which will be amenable to ligand optimisation to maximise asymmetric induction.

Experimental

All dry glassware was oven-dried at 150 °C overnight or flame-dried prior to use. All reactions in anhydrous solvent were carried out under a dry nitrogen atmosphere. Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}). Visualisation was accomplished with UV light (254 nm), acidic ammonium molybdate(IV) or potassium permanganate. Flash column chromatography was performed on Merck Kieselgel 60 (200–300 mesh) under gentle pressure from hand bellows.

^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX250, JEOL-GSL270 and Bruker DRX300 spectrometers. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane, and are referenced to (residual protic) solvent; coupling constants (J) are expressed in Hertz. ^{19}F NMR spectra were recorded on Bruker ARX250 spectrometer. Infrared spectra were recorded on a Perkin Elmer 683 Infrared Spectrometer. Mass spectra were recorded on a VG Autospec Q or Micromass Platform II spectrometer under chemical ionisation (CI) with ammonia. Optical rotations were measured with a Perkin-Elmer 141 and an Optical Activity AA1000 polarimeter with a path length of 1 dm at 598 nm and concentration c measured in g per 100 ml. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected.

Tetrahydrofuran and diethyl ether for use as reaction solvents were dried by prolonged heating under reflux over and distillation from sodium–benzophenone ketyl.

2-Methyl-1,3-cyclohexanedione[17]

1,3-Cyclohexanedione (16.8 g, 150 mmol) was dissolved in 5 M aqueous NaOH (30 ml, 150 mmol) at 0 °C. Iodomethane (42.6 g, 300 mmol) was added to the resulting red/brown solution in one portion. The ice bath was removed and the mixture was heated at 65 °C for 24 h, then allowed to cool to room temperature. The beige/orange solid was filtered, and washed with petrol (100 ml) and a minimum amount of cold water until a pale beige solid was obtained. This was dried *in vacuo* to give 2-methyl-1,3-cyclohexanedione (12.3 g, 97.5 mmol, 65%) which was used in the next step without further purification: mp 198–200 °C (lit.[17] 204–205 °C). ^{1}H NMR (270 MHz; DMSO-d_6; 100% enol tautomer) δ_H 1.53 (3H, s, CH_3), 1.80 (2H, quintet, J 6.5, 5-H) and 2.29 (4H, t, J 6.5, 4-H and 6-H). ^{13}C NMR (67.5 MHz; DMSO-d_6) δ_C 7.7 (CH_3), 21.0 (5-C), 33.0 (br, 4-C and 6-C) and 110.0 (1-C and 3-C) (C2 signal not observed).

2-Benzyl-1,3-cyclohexanedione

Prepared by the same procedure as above from 1,3-cyclohexanedione (14.0 g, 125 mmol), benzyl bromide (32.0 g, 187.5 mmol) and 5 M aqueous NaOH (25 ml, 125 mmol), except that the mixture was heated at 100 °C for 3 h. The solid formed was filtered and washed successively with petrol (150 ml), a minimum amount of cold water and cold ether until a pale beige solid was obtained (19.2 g, 94.9 mmol, 76%). This was used in the next step without further purification: mp 178–180 °C (lit.[23] 184–185 °C from toluene). IR ν_{max}(KBr)/cm^{-1} 3500–3000br, 2958w, 2927w, 1710s (C=O), 1602w, 1232w, 1180w. ^{1}H NMR (270 MHz; DMSO-d_6 + acetone-d_6; 100% enol tautomer) δ_H 1.88 (2H, quintet, J 6.0, 5-H), 2.38 (4H, t, J 6.0, 4-H and 6-H), 3.55 (2H, s, CH_2Ph) and 7.00–7.30 (5H, m, Ph). ^{13}C NMR (67.5 MHz; DMSO-d_6 + acetone-d_6) δ_C 21.0 (5-C), 27.5 (CH_2Ph), 33.0 (br, 4-C and 6-C), 114.8 (1-C and 3-C), 125.2 (Ar CH), 127.9 (Ar CH), 128.7 (Ar CH) and 142.5 (Ar C) (C2 signal not observed).

2-Allyl-2-methyl-1,3-cyclopentanedione[17] 8a

Allyl bromide (14.5 g, 120 mmol) and Bu_4NI (222 mg, 0.6 mmol) was added to a solution of 2-methyl-1,3-cyclopentanedione (Aldrich; 7.0 g, 60 mmol) in 1 M aqueous NaOH (60 ml, 60 mmol). The mixture was stirred vigorously for 72 h. The organic layer was separated and the aqueous layer was extracted with DCM (2 × 35 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. Vacuum distillation of the crude material gave the title compound (7.7 g, 50.6 mmol, 84%) as a colourless oil: bp 88–90 °C (4 mmHg) (lit.[17] 65 °C, 2 mmHg). IR ν_{max}(KBr/film)/cm^{-1} 3079w, 2979s, 2931s, 2873w,

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1764w, 1725s (C=O), 1641w, 1452m, 1419m, 1068s and 1029s. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 0.95 (3H, s, CH_3), 2.19 (2H, d, *J* 7.5, $CH_2CH{=}CH_2$), 2.47–2.70 (4H, m, 2 × CH_2CO), 4.87–4.94 (2H, m, $CH{=}CH_2$) and 5.44 (1H, ddt, *J* 16.0, 11.0 and 7.5, $CH{=}CH_2$). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 18.6 (CH_3), 35.3 (CH_2CO), 40.0 ($CH_2CH{=}$), 56.6 (C), 119.7 ($=CH_2$), 131.5 (CH=) and 216.2 (C=O).

2-Allyl-2-methyl-1,3-cyclohexanedione 8b

Prepared as for **8a** from allyl bromide (23.6 g, 195 mmol), Bu_4NI (362 mg, 0.98 mmol), 2-methyl-1,3-cyclohexanedione (12.3 g, 97.5 mmol) and 1 M aqueous NaOH (97.5 ml, 97.5 mmol). Vacuum distillation of the crude material gave the title compound (12.9 g, 77.6 mmol, 80%) as a pale yellow oil: bp 100–102 °C (1 mmHg) (lit.[24] 63 °C, 0.23 mmHg). IR ν_{max}(KBr/film)/cm^{-1} 3079w, 2967s, 2940s, 2877s, 1724m (C=O), 1693s (C=O), 1454m, 1321m, 1025m and 921m. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.22 (3H, s, CH_3), 1.78–2.07 (2H, m, CH_2CH_2CO), 2.52 (2H, dt, *J* 7.0 and 1.0, $CH_2CH{=}CH_2$), 2.55–2.72 (4H, m, 2 × CH_2CO), 5.00–5.08 (2H, m, $CH{=}CH_2$) and 5.56 (1H, ddt, *J* 17.5, 9.5 and 7.0, $CH{=}CH_2$). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 17.5 (CH_2CH_2CO), 19.3 (CH_3), 38.1 (CH_2CO), 41.2 ($CH_2CH{=}$), 65.1 (C), 119.1 ($=CH_2$), 132.2 (CH=) and 209.8 (C=O).

2-Allyl-2-benzyl-1,3-cyclohexanedione 8c

Prepared as for **8a** from allyl bromide (9.6 g, 79.2 mmol), Bu_4NI (148 mg, 0.4 mmol), 2-benzyl-1,3-cyclohexanedione (8.0 g, 39.6 mmol) and 1 M aqueous NaOH (39.6 ml, 39.6 mmol). Recrystallisation of the crude material from ether yielded the title compound (5.4 g, 22.3 mmol, 56%) as a pale yellow crystalline solid: mp 57–59 °C (lit.[25] 62 °C). IR ν_{max}(KBr/film)/cm^{-1} 3059w, 3034w, 2960w, 2934w, 2884w, 1720m (C=O), 1694s (C=O), 1457m, 1340m, 930s and 705s. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.05–1.20 (1H, m, CH_2CH_2CO), 1.52–1.68 (1H, m, CH_2CH_2CO), 2.07 (2H, ddd, *J* 17.0, 8.0 and 5.0, CH_2CO), 2.33 (2H, ddd, *J* 17.0, 8.5 and 5.0, CH_2CO), 2.62 (2H, d, *J* 7.5, $CH_2CH{=}CH_2$), 3.08 (2H, s, CH_2Ph), 5.02 (1H, d, *J* 10.0, $CH{=}CH_2$ *cis*), 5.04 (1H, d, *J* 17.0, $CH{=}CH_2$ *trans*) and 5.53 (1H, ddt, *J* 17.0, 10.0 and 7.5, $CH{=}CH_2$), 6.93–7.05 (2H, m, Ph) and 7.15–7.25 (3H, m, Ph). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 14.9 (CH_2CH_2CO), 40.6 (CH_2CO), 42.3 (CH_2), 43.9 (CH_2), 68.7 (C), 118.9 ($=CH_2$), 126.6, 128.0, 129.4 (CH of Ph), 132.0 (CH=), 136.1 (C of Ph) and 211.1 (C=O).

General procedure for the preparation of iododiketones

A 2.0 M solution of $BH_3{\cdot}SMe_2$ in THF (1.2 eq.) was carefully added *via* a syringe to a solution of freshly distilled cyclohexene (2.52 eq.) in dry THF (0.6 ml per mmol of $BH_3{\cdot}SMe_2$) at 0 °C. A thick white precipitate appeared after *ca.* 5–10 minutes, indicating the formation of dicyclohexylborane. The mixture was stirred at that temperature for 1 h, then a solution of alkene **8** (1.0 eq.) in dry THF (0.5 ml per mmol of **8**) at 0 °C was added dropwise *via* a cannula (followed by a THF rinse, 0.3 ml per mmol of **8**). Stirring was continued at 0 °C for 1.5 h and then at room temperature for 1.5 h, during which time the precipitate was consumed. The mixture was then cooled again to 0 °C and a solution of sodium acetate (2.4 eq.) in methanol (1 ml per mmol of NaOAc) was slowly added, immediately followed by dropwise addition of a solution of iodine (1.1 eq.) in methanol (1 ml per mmol of iodine), both *via* a cannula. The resulting red/brown solution was stirred at room temperature for 18 h and then quenched by a slow addition of saturated aqueous sodium thiosulfate until the mixture turned pale yellow. This was stirred for 15 minutes, then diluted with water (5 ml per mmol of **8**) and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (gradient elution, 10% petroleum ether–DCM to DCM).

2-(3-Iodopropyl)-2-methyl-1,3-cyclopentanedione 9a. Prepared and purified according to the general procedure from **8a** (2.5 g, 16.4 mmol), cyclohexene (3.39 g, 41.3 mmol), $BH_3{\cdot}SMe_2$ (9.85 ml of 2.0 M solution in THF, 19.7 mmol), sodium acetate (3.23 g, 39.4 mmol) and iodine (4.58 g, 18.0 mmol), except that the reaction mixture was stirred at 0 °C for 3 h after the addition of **8a** to dicyclohexylborane. The product was obtained as a pale yellow oil (1.5 g, 5.7 mmol, 35%). IR ν_{max}(KBr/film)/cm^{-1} 2924s, 1716s (C=O), 1451m, 1418m, 1231m, 1074m and 991m. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.08 (3H, s, CH_3), 1.12–1.32 (2H, br m, CH_2), 1.59–1.72 (2H, m, CH_2), 2.64–2.84 (4H, m, 2 × CH_2CO) and 3.00–3.06 (2H, m, CH_2I). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 5.2 (CH_2I), 19.2 (CH_3), 28.4 (CH_2), 35.1 (CH_2), 35.8 (CH_2CO), 56.1 (C) and 215.9 (C=O). LRMS (CI^+/NH_3): *m*/*z* (%) = 298 ([M + NH_4]$^+$, 100), 172 (38), 153 (75), 142 (25) and 125 (21). HRMS (CI^+/NH_3): *m*/*z* calcd for [M + NH_4]$^+$: $C_9H_{17}INO_2$ = 298.0304. Found 298.0302.

2-(3-Iodopropyl)-2-methyl-1,3-cyclohexanedione 9b. Prepared and purified according to the general procedure from **8b** (5.0 g, 30.1 mmol), cyclohexene (6.24 g, 75.9 mmol), $BH_3{\cdot}SMe_2$ (18.1 ml of 2.0 M solution in THF, 36.1 mmol), sodium acetate (5.92 g, 72.2 mmol) and iodine (8.4 g, 33.1 mmol). The product was obtained as a yellow oil (4.85 g, 16.5 mmol, 55%). IR ν_{max}(KBr/film)/cm^{-1} 2958m, 1725s (C=O), 1694s (C=O), 1456m, 1426m, 1375m, 1218m and 1025m. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.23 (3H, s, CH_3), 1.54–1.65 (2H, m, 1-H or 2-H), 1.79–2.02 (4H, m, CH_2CH_2CO and 1-H or 2-H), 2.55–2.73 (4H, m, CH_2CO) and 3.08 (2H, t, *J* 6.5, CH_2I). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 5.9 (CH_2I), 17.7 (CH_2CH_2CO), 20.2 (CH_3), 28.7 (CH_2), 37.2 (CH_2), 37.9 (2 × CH_2CO), 65.0 (C) and 209.9 (C=O). LRMS (CI^+/NH_3): *m*/*z* (%) = 312 ([M + NH_4]$^+$, 100), 172 (55) and 167 (100). HRMS (CI^+/NH_3): *m*/*z* calcd for [M + NH_4]$^+$: $C_{10}H_{19}INO_2$ = 312.0461. Found 312.0474.

2-Benzyl-2-(3-iodopropyl)-1,3-cyclohexanedione 9c. Prepared and purified according to the general procedure from **8c** (5.28 g, 21.8 mmol), cyclohexene (4.52 g, 55.0 mmol), $BH_3{\cdot}SMe_2$ (13.1 ml of 2.0 M solution in THF, 26.2 mmol), sodium acetate (4.30 g, 52.3 mmol) and iodine (6.10 g, 24.0 mmol). The product was obtained as a yellow oil (3.40 g, 9.2 mmol, 42%): IR ν_{max}(KBr/film)/cm^{-1} 3061w, 3027w, 2949w, 2887w, 1717s (C=O), 1690s (C=O), 1438m, 1176m, 761s and 706s. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.19–1.34 (1H, m, CH_2CH_2CO), 1.40–1.70 (3H, m, CH_2CH_2CO and 1-H or 2-H), 1.95–2.00 (2H, m, 1-H or 2-H), 2.09 (2H, ddd, *J* 17.0, 9.0 and 5.0, CH_2CO), 2.40 (2H, ddd, *J* 17.0, 7.5 and 4.5, CH_2CO), 3.03 (2H, t, *J* 7.0, CH_2I), 3.04 (2H, s, CH_2Ph), 6.93–6.99 (2H, m, Ph) and 7.15–7.26 (3H, m, Ph). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 4.8 (CH_2I), 15.4 (CH_2CH_2CO), 29.1 (CH_2), 38.3 (CH_2), 40.4 (CH_2CO), 44.8 (CH_2Ph), 68.2 (C), 126.9,

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128.2, 129.4 (CH of Ph), 135.7 (C of Ph) and 211.4 (C=O). LRMS (CI^+/NH_3): m/z (%) = 388 ($[M + NH_4]^+$, 100), 262 (86) and 243 (8). HRMS (CI^+/NH_3): m/z calcd for $[M + NH_4]^+$: $C_{16}H_{23}INO_2$ = 388.0774. Found: 388.0768.

General procedure for the preparation of azidodiketones 4a–c

Caution: azides are potentially explosive and should be handled and treated with appropriate precautions.[19] All reactions and manipulations of azides were carried out behind a blast shield.

A solution of sodium azide (5 eq.) in water (1.25 ml per mmol of sodium azide) was added to the solution of iodopropyl cycloalkyldione **9** (1 eq.) and Bu_4NI (0.1 eq.) in acetone (7.3 ml per mmol of **9**). The resulting homogeneous mixture was stirred at room temperature for 72 h—if the mixture was not homogeneous, an additional amount of water and/or acetone was slowly added until the mixture became homogeneous. The mixture was then diluted with water (6 ml per mmol of **9**) and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (50% ether–petroleum ether).

2-(3-Azidopropyl)-2-methyl-1,3-cyclopentanedione 4a. Prepared and purified according to the general procedure from **9a** (1.5 g, 5.7 mmol), sodium azide (1.85 g, 28.5 mmol) and Bu_4NI (22 mg, 0.06 mmol). The product was obtained as a yellow oil (950 mg, 4.85 mmol, 85%). IR ν_{max}(KBr/film)/cm^{-1} 2929s, 2856w, 2100s (N_3), 1762w (C=O), 1722s (C=O), 1452m, 1421m, 1263m and 1062m. ^1H NMR (270 MHz; $CDCl_3$) δ_H 1.12 (3H, s, CH_3), 1.36–1.39 (2H, m, CH_2), 1.65–1.71 (2H, m, CH_2), 2.66–2.88 (4H, m, 2 × CH_2CO) and 3.21 (2H, t, J 6.5, CH_2N_3). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 19.7 (CH_3), 24.0 (CH_2), 31.7 (CH_2), 35.1 (CH_2CO), 51.2 (CH_2N_3), 56.2 (C) and 216.0 (C=O). LRMS (CI^+/NH_3): m/z (%) = 213 ($[M + NH_4]^+$, 100), 185 (40) and 168 (84). HRMS (CI^+/NH_3): m/z calcd for ($[M + NH_4]^+$) $C_9H_{17}N_4O_2$ = 213.1352. Found 213.1366.

2-(3-Azidopropyl)-2-methyl-1,3-cyclohexanedione 4b. Prepared and purified according to the general procedure from **9b** (4.82 g, 16.4 mmol), sodium azide (5.33 g, 82.0 mmol) and Bu_4NI (59 mg, 0.16 mmol). The product was obtained as a pale yellow oil (3.0 g, 14.3 mmol, 87%): IR ν_{max}(KBr/film)/cm^{-1} 2950s, 2933s, 2875w, 2098s (N_3), 1725s (C=O), 1695s (C=O), 1459m, 1427m, 1263m and 1024m. ^1H NMR (270 MHz; $CDCl_3$) δ_H 1.21 (3H, s, CH_3), 1.30–1.41 (2H, m, CH_2), 1.75–1.86 (2H, m, CH_2), 1.88–1.97 (2H, m, CH_2), 2.63 (4H, t, J 6.5, 2 × CH_2CO) and 3.20 (2H, t, J 6.5, CH_2N_3). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 17.6 (CH_2CH_2CO), 20.8 (CH_3), 24.4 (CH_2), 33.1 (CH_2), 37.9 (CH_2CO), 51.3 (CH_2N_3), 65.1 (C) and 210.1 (C=O). LRMS (CI^+/NH_3): m/z (%) = 227 ([M + $NH_4]^+$, 100), 199 (75), 184 (25), 167 (87) and 153 (32). HRMS (CI^+/NH_3): m/z calcd for ($[M + NH_4]^+$) $C_{10}H_{19}N_4O_2$ = 227.1508. Found 227.1506.

2-(3-Azidopropyl)-2-benzyl-1,3-cyclohexanedione 4c. Prepared and purified according to the general procedure from **9c** (3.36 g, 9.1 mmol), sodium azide (2.96 g, 45.5 mmol) and Bu_4NI (34 mg, 0.09 mmol). The product was obtained as an oil, which solidified on standing in a freezer (2.05 g, 7.2 mmol, 79%): IR ν_{max}(KBr/film)/cm^{-1} 3063w, 3031w, 2933s, 2886m, 2098s (N_3), 1722s (C=O), 1694s (C=O), 1455m, 1259m, 1032m, 762m and 703s. ^1H NMR (270 MHz; $CDCl_3$) δ_H 1.23–1.40 (3H, m, CH_2CH_2CO and 1-H or 2-H), 1.57–1.71 (1H, m, CH_2CH_2CO), 1.92–1.98 (2H, m, 1-H or 2-H), 2.13 (2H, ddd, J 17.0, 9.0 and 5.0, CH_2CO), 2.43 (2H, ddd, J 17.0, 7.5 and 5.0, CH_2CO), 3.06 (2H, s, CH_2Ph), 3.20 (2H, t, J 7.0, CH_2N_3), 6.96–7.01 (2H, m, Ph) and 7.20–7.28 (3H, m, Ph). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 15.6 (CH_2CH_2CO), 24.8 (CH_2), 34.3 (CH_2), 40.6 (CH_2CO), 45.3 (CH_2Ph), 51.1 (CH_2N_3), 68.7 (C), 127.1, 128.4, 129.6 (CH of Ph), 135.8 (C of Ph) and 211.7 (C=O). LRMS (CI^+/NH_3): m/z (%) = 303 ($[M + NH_4]^+$, 100) and 258 (96). HRMS (CI^+/NH_3): m/z calcd for ($[M + NH_4]^+$) $C_{16}H_{23}N_4O_2$ = 303.1821. Found 303.1823.

General procedure for the Schmidt rearrangement of azidodiketones 4 utilising achiral Lewis acids

Lewis acid (2.5 eq. unless otherwise stated) was added to a solution of an azidodiketone **4** (1.0 eq.) in dry ether (10 ml per mmol of **4**) and the reaction was stirred at ambient temperature. The progress of the reaction was monitored by the disappearance of the azide stretch in the IR spectrum. After the reaction was complete (or at 72 hours, whichever was sooner), saturated $NaHCO_3$ solution was slowly added to quench the excess Lewis acid and the resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (methanol–DCM).

Preparation of 8a-methylhexahydroindolizine-5,8-dione 6a. Prepared and purified according to the general procedure from **4a** (100 mg, 0.51 mmol) and $BF_3{\cdot}OEt_2$ (0.27 ml, 2 mmol, 4 eq.) or $EtAlCl_2$ (1.0 M solution in DCM, 1.28 ml) or $TiCl_4$ (1.0 M solution in DCM, 1.28 ml). The reaction was complete within 24, 6 and 1 h respectively. The product was obtained after flash chromatography (56, 71 and 76 mg, 65, 83 and 89% respectively) as an oil: IR ν_{max}(KBr/film)/cm^{-1} 2981m, 2933m, 2888m, 1722s (C=O ketone), 1654s (C=O amide), 1430m, 1191m, 1141m and 1118m. ^1H NMR (300 MHz; $CDCl_3$) δ_H 1.34 (3H, s, CH_3), 1.86–2.02 (4H, m, CH_2), 2.58–2.66 (3H, m, CH_2), 2.71–2.85 (1H, m, CH_2), 3.49–3.58 (1H, m, 3-H) and 3.61–3.70 (1H, m, 3-H). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 20.7 (CH_2), 23.6 (CH_3), 30.0 (CH_2), 34.3 (CH_2), 35.7 (CH_2), 45.0 (3-C), 69.1 (8a-C), 168.2 (5-C) and 209.6 (8-C). LRMS (CI^+/NH_3): m/z (%) = 185 ($[M + NH_4]^+$, 80), 168 ($[M + H]^+$, 100). HRMS (CI^+/NH_3): m/z calcd for ($[M + H]^+$) $C_9H_{14}NO_2$ = 168.1025. Found 168.1020.

Preparation of 9a-methylhexahydropyrrolo[1,2-*a*]azepine-5,9-dione 6b. Prepared and purified according to the general procedure from **4b** (100 mg, 0.48 mmol) and $BF_3{\cdot}OEt_2$ (0.25 ml, 1.92 mmol, 4 eq.) or $EtAlCl_2$ (1.0 M solution in DCM, 1.2 ml) or $TiCl_4$ (1.0 M solution in DCM, 0.53 ml, 1.1 eq.). The reaction was complete within 24, 6 and 1 h respectively. The product was obtained as a pale yellow solid (74, 70 and 58 mg, 85, 80 and 67% respectively): mp 63–65 °C. IR ν_{max}(KBr/film)/cm^{-1} 2954s, 2921s, 2858s, 1718s (C=O ketone), 1648s (C=O amide), 1461m, 1407m, 1288w, 1105m and 1037m. ^1H NMR (300 MHz; $CDCl_3$) δ_H 1.40 (3H, s, CH_3), 1.77–1.82 (1H, m, CH_2), 1.85–2.01 (4H, m, CH_2), 2.02–2.16 (1H, m, CH_2), 2.26–2.40 (3H, m, CH_2 and 6-H or 8-H), 2.87 (1H, td, J 11.0 and 9.5, 6-H or 8-H), 3.51–3.63 (1H, m, 3-H) and 3.68–3.75 (1H, m, 3-H). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 20.5 (CH_2), 21.4 (CH_3), 22.7 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 38.5 (CH_2), 46.8 (3-C), 71.4 (9a-C), 170.4 (5-C) and 212.5 (9-C). LRMS (CI^+/NH_3): m/z (%) = 199 ($[M + NH_4]^+$, 12) 182

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([M + H]$^+$, 100), and 138 (14). HRMS (CI$^+$/NH$_3$): *m/z* calcd for ([M + H]$^+$) $C_{10}H_{16}NO_2$ = 182.1181. Found 182.1181.

Preparation of 9a-benzylhexahydropyrrolo[1,2-*a*]azepine-5,9-dione 6c. Prepared and purified according to the general procedure from **4c** (117 mg, 0.41 mmol) and $EtAlCl_2$ (1.0 M solution in DCM, 1 ml). The product was obtained as a pale yellow solid (92 mg, 87%): mp 158–160 °C; IR ν_{max}(KBr/film)/cm^{-1} 3060w, 3030w, 2945m, 2886m, 1718s (C=O ketone), 1649s (C=O amide), 1460m, 1268m, 1035m, 765m and 702s. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.36–1.59 (2H, m, CH_2), 1.72–1.87 (2H, m, CH_2), 1.89–2.04 (4H, m, CH_2), 2.22 (1H, dd, *J* 11.0 and 7.5, 6-H or 8-H), 2.78 (1H, td, *J* 11.5 and 8.5, 8-H), 2.86 (1H, d, *J* 13.5, C*H*$_a$H$_b$Ph), 3.36 (1H, d, *J* 13.5, CH$_a$*H*$_b$Ph), 3.47 (1H, ddd, *J* 12.5, 9.5 and 2.5, 3-H) and 3.65 (1H, ddd, *J* 12.5, 9.5 and 8.5, 3-H) and 7.04–7.25 (5H, m, Ph). ^{13}C NMR (67.5 MHz; $CDCl_3$) δ_C 20.9 (CH_2), 23.0 (CH_2), 32.5 (CH_2), 34.9 (CH_2), 38.0 (CH_2), 39.6 (CH_2), 47.6 (3-C), 75.5 (9a-C), 127.2 (CH of Ph), 128.6 (CH of Ph), 130.5 (CH of Ph), 136.4 (C of Ph), 171.5 (5-C) and 211.0 (9-C). LRMS (CI$^+$/NH$_3$): *m/z* (%) = 258 ([M + H]$^+$, 100) and 166 (14). HRMS (CI$^+$/NH$_3$): *m/z* calcd for ([M + H]$^+$) $C_{16}H_{20}NO_2$ = 258.1494. Found 258.1498.

General procedure for the reduction of lactams 6a–c

Sodium borohydride (2.5 eq.) was added to the solution of a bicyclic lactam **6** (1.0 eq.) in methanol (15 ml per mmol of **6**) at room temperature in one portion. The reaction was stirred for 45 minutes and then quenched with water (0.1 ml per mmol of **6**). The mixture was evaporated to dryness and the residue was pre-absorbed on silica gel. The two diastereoisomeric products **11** and **12** were separated by flash chromatography.

Preparation of 8-hydroxy-8a-methylhexahydroindolizine-5-one 10a and 11a. Prepared according to the general procedure from **6a** (31 mg, 0.185 mmol) and $NaBH_4$ (17.5 mg, 0.463 mmol). The ^{1}H NMR spectrum of the crude material showed a diastereomeric ratio of ~91 : 9. Flash chromatography (60% acetone–DCM) gave the major diastereoisomer (26 mg, 83%): IR ν_{max}(NaCl/film)/cm^{-1} 3392br (O–H), 2973m, 2888m, 1606s (C=O), 1459m, 1413m, 1099m and 1054m. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 1.16 (3H, s, CH_3), 1.66 (1H, td, *J* 11.5 and 8.5, 6-H), 1.87–2.00 (4H, m, 2-H and 7-H), 2.01–2.12 (1H, m, 6-H), 2.40 (1H, ddd, *J* 18.5, 9.5 and 9.0, 1-H), 2.52 (1H, ddd, *J* 18.5, 7.5 and 2.5, 1-H), 3.38 (1H, br s, OH), 3.41–3.56 (1H, m, 3-H) and 3.59–3.67 (2H, m, 3-H and 8-H). ^{13}C NMR (75.5 MHz; $CDCl_3$) δ_C 18.3 (CH_3), 20.7 (2-C or 7-C), 25.9 (2-C or 7-C), 29.5 (1-C or 6-C), 39.3 (1-C or 6-C), 45.3 (3-C), 64.2 (8a-C), 74.3 (8-C) and 168.4 (5-C). LRMS (CI$^+$/NH$_3$): *m/z* (%) = 170 ([M + H]$^+$, 100) and 125 (5). HRMS (CI$^+$/NH$_3$): *m/z* calcd for ([M + H]$^+$) $C_9H_{16}NO_2$ = 170.1181. Found 170.1179. The minor isomer was not isolated following chromatography.

Preparation of 9-hydroxy-9a-methyloctahydropyrrolo[1,2-*a*]-azepine-5-one 10b and 11b. Prepared according to the general procedure from **6b** (54 mg, 0.3 mmol) and $NaBH_4$ (28 mg, 0.75 mmol). The ^{1}H NMR spectrum of the crude material showed a diastereomeric ratio of ~71 : 29. Flash chromatography (30% acetone–DCM) gave the major diastereoisomer (30 mg, 55%): IR ν_{max}(NaCl/film)/cm^{-1} 3389br (O–H), 2971s, 2939s, 2876s, 1601s (C=O), 1443s, 1051m and 1026m. ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.28 (3H, s, CH_3), 1.48–2.12 (8H, m, 1-H, 2-H, 7-H and 8-H), 2.40–2.60 (3H, m, 6-H and OH), 3.28–3.44 (2H, m, 3-H and 9-H) and 3.77–3.85 (1H, m, 3-H). ^{13}C NMR δ_C (67.5 MHz; $CDCl_3$) 18.3 (CH_3), 20.7 (1-C), 21.7 (7-C), 34.1 (8-C), 37.0 (6-C), 42.1 (2-C), 49.4 (3-C), 65.2 (9a-C), 77.5 (9-C) and 173.6 (5-C). LRMS (CI$^+$/NH$_3$): *m/z* (%) = 184 ([M + H]$^+$, 100). HRMS (CI$^+$/NH$_3$): *m/z* calcd for ([M + H]$^+$) $C_{10}H_{18}NO_2$ = 184.1338. Found 184.1340. Further elution gave the minor diastereoisomer (11 mg, 20%): ^{1}H NMR (270 MHz; $CDCl_3$) δ_H 1.35 (3H, s, CH_3), 1.57–2.06 (8H, m, 1-H, 2-H, 7-H and 8-H), 2.49–2.66 (3H, m, 6-H and OH), 3.43 (1H, ddd, *J* 12.0, 9.5 and 7.5, 3-H) and 3.73–3.82 (2H, m, 3-H and 9-H); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ_C 16.7 (CH_3), 21.4 (1-C), 23.7 (7-C), 30.9 (8-C), 37.4 (6-C), 39.7 (2-C), 50.1 (3-C), 65.2 (9a-C), 72.3 (9-C) and 173.4 (5-C).

Preparation of 9a-benzyl-9-hydroxyoctahydropyrrolo[1,2-*a*]-azepine-5-one 10c and 11c. Prepared according to the general procedure from **6c** (92 mg, 0.36 mmol) and $NaBH_4$ (34 mg, 0.9 mmol). The ^{1}H NMR spectrum of the crude material showed a diastereomeric ratio of 71 : 29. Flash chromatography (25% acetone–DCM) gave the major diastereoisomer (51.4 mg, 55%): IR ν_{max}(NaCl/film)/cm^{-1} 3394br (O–H), 2960m, 2933m, 2869m, 1598s (C=O), 1452m, 1265w, 748w and 701w. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 0.32–0.50 (1H, m, 2-H), 1.26–1.40 (1H, m, 2-H), 1.65–1.80 (1H, m, 7-H), 1.92–2.26 (5H, m, 1-H, 1 × 7-H and 8-H), 2.74–2.90 (2H, m, 6-H), 2.88 (1H, d, *J* 14.0, C*H*$_a$H$_b$Ph), 3.21 (1H, br s, OH), 3.31–3.41 (2H, m, 3-H), 3.39 (1H, d, *J* 14.0, CH$_a$*H*$_b$Ph), 3.55 (1H, dt, *J* 10.0 and 5.0, 9-H) and 7.09–7.28 (5H, m, Ph). ^{13}C NMR (75.5 MHz; $CDCl_3$) δ_C 19.9 (2-C), 22.0 (7-C), 33.7 (8-C), 36.1 (*C*H$_2$Ph), 37.3 (6-C), 39.0 (1-C), 50.1 (3-C), 68.7 (9a-C), 78.1 (9-C), 126.7 (CH of Ph), 128.5 (CH of Ph), 130.3 (CH of Ph), 137.4 (C of Ph) and 173.9 (5-C). LRMS (CI$^+$/NH$_3$): *m/z* (%) = 260 ([M + H]$^+$, 100) and 168 (26). HRMS (CI$^+$/NH$_3$): *m/z* calcd for ([M + H]$^+$) $C_{16}H_{22}NO_2$ = 260.1651. Found 260.1656. Further elution gave the minor diastereoisomer (21.7 mg, 23%): ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 0.69–0.86 (1H, m, 2-H), 1.45–1.60 (1H, m, 2-H), 1.69–1.84 (1H, m, 7-H), 1.90–2.04 (3H, m, 1-H, 7-H and 8-H), 2.18–2.25 (2H, m, 8-H and OH), 2.39–2.50 (1H, m, 1-H), 2.61 (1H, d, *J* 14.0, C*H*$_a$H$_b$Ph), 2.62–2.88 (2H, m, 6-H), 3.32–3.50 (2H, m, 3-H), 3.47 (1H, d, *J* 14.0, CH$_a$*H*$_b$Ph), 3.80–3.97 (1H, br m, 9-H) and 7.12–7.33 (5H, m, Ph). ^{13}C NMR (75.5 MHz; $CDCl_3$) δ_C 17.1 (7-C), 20.8 (2-C), 30.6 (8-C), 36.0 (1-C), 37.5 (6-C), 41.3 (*C*H$_2$Ph), 50.6 (3-C), 68.9 (9a-C), 72.6 (9-C), 126.9 (CH of Ph), 128.5 (CH of Ph), 130.2 (CH of Ph), 136.8 (C of Ph) and 173.4 (5-C).

General procedure for desymmetrising Schmidt-type reactions mediated by (−)-menthoxyaluminium dichloride

A 1.0 M solution of $EtAlCl_2$ (1 eq.) was added to a solution of (−)-menthol (1.2 eq.) in dry hexane (4.5 ml per mmol of azidodiketone **4**). After stirring at room temperature for 30 minutes, a solution of an azidodiketone **4** (1 eq.) in dry toluene (4.5 ml per mmol of **4**) was added to the mixture *via* a cannula. The reaction was stirred for 72 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated and the residue was purified by flash chromatography (3% methanol–DCM).

Reaction with 4a. The reaction was carried out according to the general procedure from **4a** (124.4 mg, 0.637 mmol), $EtAlCl_2$ (1 M solution in DCM, 637 µl, 0.637 mmol) and (−)-menthol (119 mg, 0.764 mmol). The ^{1}H NMR spectrum of the crude

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mixture showed a 40% conversion. Flash chromatography of the crude material yielded **6a** (36.4 mg, 35%): ee = 0% determined by ^{1}H NMR spectrum of the Mosher's ester of alcohol **10a** following reduction: ^{1}H NMR (270 MHz; $CDCl_3$) δ_H (*inter alia*) 1.11 (s, CH_3, 50%) and 1.41 (s, CH_3, 50%).

Reaction with 4b. The reaction was carried out according to the general procedure from **4b** (200 mg, 0.96 mmol), $EtAlCl_2$ (1 M solution in DCM, 0.96 ml, 0.96 mmol) and (−)-menthol (180 mg, 1.15 mmol). The ^{1}H NMR spectrum of the crude mixture showed a 67% conversion. Flash chromatography of the crude material yielded **6b** (87 mg, 50%): $[\alpha]^{21}_D$ +4.4 (*c* 1 in DCM); ee = 5% determined by ^{19}F NMR spectrum of the Mosher's ester of alcohol **10b** following reduction: ^{19}F NMR (250 MHz; $CDCl_3$) δ_F −75.32 (52.5%) and −75.20 (47.5%).

Reaction with 4c. The reaction was carried out according to the general procedure from **4c** (58.4 mg, 0.205 mmol), $EtAlCl_2$ (1 M solution in DCM, 205 µl, 0.205 mmol) and (−)-menthol (38 mg, 0.246 mmol). The ^{1}H NMR spectrum of the crude mixture showed a 40% conversion. Flash chromatography of the crude material yielded **6c** (14 mg, 27%); ee = 0% determined by ^{19}F NMR spectrum of the Mosher's ester of alcohol **10c** following reduction: ^{19}F NMR (250 MHz; $CDCl_3$) δ_F −74.95 (50%) and −75.02 (50%).

General procedure for desymmetrising Schmidt reaction mediated by (*S*)-binaphthoxyaluminium chloride

A 1 M solution of Me_2AlCl (1 eq.) was added dropwise to a solution of (*S*)-BINOL (1.2 eq.) in DCM (12 ml per mmol of azidodiketone **4**). The evolution of gas and the formation of a white precipitate were observed. The mixture was stirred at room temperature for 2 h, after which DCM was removed *via* the vacuum line and toluene (6 ml per mmol of **4**) was added to the resulting residue. Then the solution of an azidodiketone **4** (1 eq.) in toluene (6 ml per mmol of **4**) was added to the chiral Lewis acid *via* a cannula and the mixture was stirred at room temperature for 72 h. The work-up, purification and determination of the enantiomeric excesses of the products were carried out according to the procedure described above.

Reaction with 4a. The reaction was carried out according to the general procedure from **4a** (100 mg, 0.51 mmol), Me_2AlCl (1 M solution in DCM, 0.51 ml, 0.51 mmol) and (*S*)-BINOL (175 mg, 0.61 mmol). The ^{1}H NMR spectrum of the crude mixture showed a 22% conversion. Flash chromatography of the crude material yielded **6a** (15 mg, 18%): $[\alpha]^{24}_D$ +26.0 (*c* 1 in DCM); ee = 6% determined by ^{1}H NMR spectroscopy of the Mosher's ester derivative as above.

Reaction with 4b. The reaction was carried out according to the general procedure from **4b** (150 mg, 0.72 mmol), Me_2AlCl (1 M solution in DCM, 0.96 ml, 0.96 mmol) and (*S*)-BINOL (247 mg, 0.86 mmol). The ^{1}H NMR spectrum of the crude mixture showed a 50% conversion. Flash chromatography of the crude material yielded **6b** (33 mg, 25%): $[\alpha]^{20}_D$ −7.1 (*c* 1 in DCM); ee = 4% determined by ^{19}F NMR spectrum of the Mosher's esters as above.

Reaction with 4c. The reaction was carried out according to the general procedure from **4c** (100 mg, 0.35 mmol), Me_2AlCl (1 M solution in DCM, 0.35 ml, 0.35 mmol) and (*S*)-BINOL (120 mg, 0.42 mmol). The ^{1}H NMR spectrum of the crude mixture showed a 14% conversion. Flash chromatography of the crude material yielded **6c** (9 mg, 10%): ee = 0% determined by ^{19}F NMR spectrum of the Mosher's esters as above.

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