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# From (-)-Quinic Acid to 8-Azabicyclo[3.2.1]octane Framework: Preparation of an Enantiopure Tropan-6α-ol

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***Abstract***: The carbon atom ring-insertion *via* pyrolysis of an α-diazo-β-hydroxy ester intermediate, in turn obtained by reaction between ethyldiazoacetate and 3,4-*O*-isopropylidene-3(*R*),4(*S*)-dihydroxycyclohexanone **2**, a chiron easily prepared through a five step sequence from D(-)-quinic acid **1**, was the key step for the construction of the cycloheptanone derivative **8**. Its transformation into azidosulfate **18** set the stage for the preparation of the *N*-protected 8-azabicyclo[3.2.1]octane derivative **22**, which, to the best of our knowledge, has been never obtained in optically pure form, as well as the tropan-6α-ol **24**, obtained by reduction with $LiAlH_4$. 

Recent investigations in these and other laboratories have revealed that (-)-quinic acid, an ubiquitous plant metabolite featuring a cyclohexane skeleton rich in functional groups as well as in asymmetric or pseudoasymmetric centres,[1] serves as an attractive and versatile chiral building block for enantioselective multistep syntheses of naturally occurring substances and related compounds.[2] Our own contributions in this area culminated in the formal syntheses of (-)-balanol, (-)-epibatidine[3] and (-)-ovalicine,[4] three structurally different naturally occurring compounds which have attracted the attention of both synthetic and medicinal chemists for their relevant pharmacological profiles. In the case of (-)-epibatidine, we were able to construct the 7-azabicyclic core through a surprisingly facile transannular cyclization involving the nucleophilic attack of an amino group to the electrophilic carbon of a cyclic sulfate moiety suitably placed regio- and stereospecifically into the quinic acid skeleton.[5] As summarized in the Scheme 1, the inner salt **II**, produced in high yield in the key step of the overall sequence, was eventually hydrolyzed to the key precursor 2-*endo*-hydroxy-7-azabicyclo[2.2.1]heptane **III** of the natural alkaloid.

As a logical extension of this work, we were intrigued to apply this chemistry to the construction of the 8-azabicyclo[3.2.1]octane framework, being particularly interested in the synthesis of derivatives bearing an oxygenated group at the 2-carbon bridge, the 6-hydroxy tropane skeleton representing a structural feature of a number of natural targets such as schizanthines, baogongteng derivatives and calystegines.[6] Moreover, there is a lack of satisfactory enantiospecific methodologies for the synthesis of tropane derivatives, despite the intense synthetic activity in this area.[7-9]

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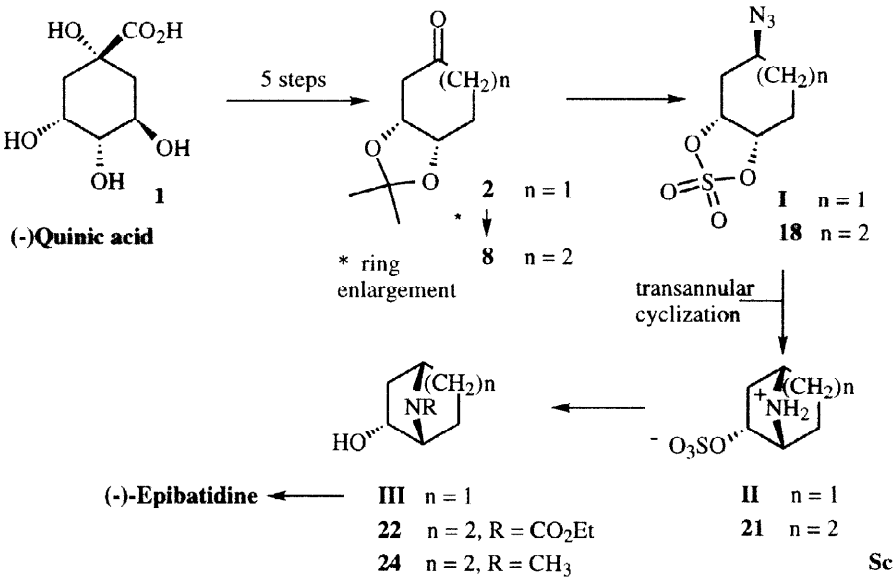
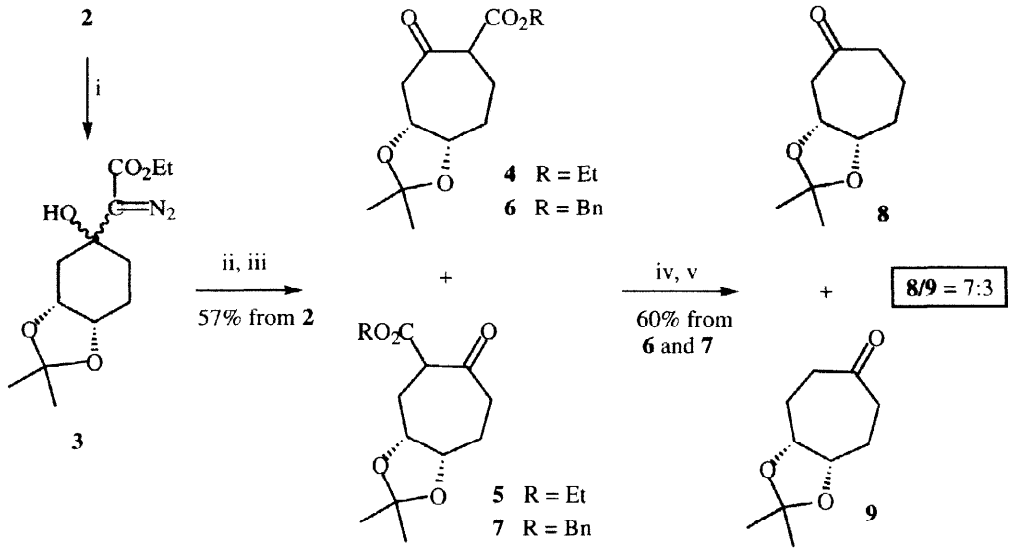



Scheme 1

Consequently, to test the possibility of effecting the desired transfomations, we envisioned the cyclic structure **18**, homolog of **I**, as the first goal. Its preparation required as the major challenge the ring enlargement of the key chiron **2**, in turn easily available from (-)-quinic acid by a published five step sequence.[10] To this end, the most direct route appeared to be the insertion of a methylene unit derived from diazomethane into **2**. However, this reaction suffered two important limitations: the formation of exocyclic epoxides and multiple ring-expansion products. On the other hand, the acid lability of the ketal moiety of **2** prevented us from carrying out a Lewis acid promoted insertion of a methylene or of a carbalkoxy unit derived from trimethylsilyldiazomethane or an alkyl diazoacetate respectively, this protocol being a rather common way to overcome these drawbacks.[11] However, Wenkert *et al.*[12] reported a methodology to accomplish ring-expansion of cyclic ketones under the influence of bases involving pyrolysis of α-diazo-β-hydroxy ester intermediates, in turn obtained by condensation of carbonyl compounds and ethyldiazoacetate. The thermal rearrangement produces β-ketoesters, although the insertions of the carbethoxy methylene unit usually occur without great discrimination between carbonyl-alkyl bonds in unsymmetrical ketones. Thus, addition of lithium diisopropylamide to an equimolar mixture of ethyl diazoacetate and ketone **2** in tetrahydrofuran solution at -78°C produced the intermediates α-diazo-β-hydroxy esters **3** in satisfactory yield (Scheme 2). Heating at reflux for 48 hours a benzene solution of the crude reaction mixture obtained after careful hydrolytic work-up and solvent removal, afforded the expected mixture of the regioisomeric β-ketoesters **4** and **5** inseparable by chromatography. Their decarbethoxylation proved to be rather troublesome both under basic or neutral conditions. Application to the mixture of **4** and **5** of both Krapcho's thermal protocol[13] or solvolytic conditions, i.e., $K_2CO_3$-MeOH, or other less common protocols reported in the literature,[14a-c] led unexpectedly to the removal of the isopropylidene unit with the formation of very polar intermediates.

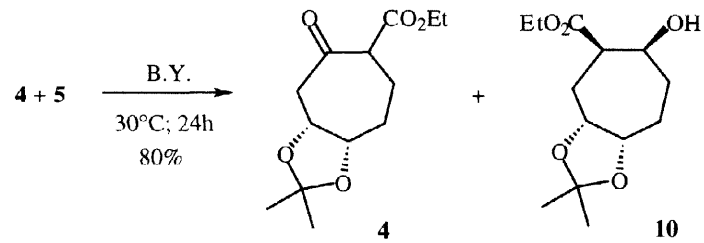
However, their transformation to the corresponding benzylesters **6** and **7**, followed by hydrogenolysis and thermal decarboxylation, gave a 7:3 mixture of cycloheptanone derivatives **8** and **9** which could be only partially separated by chromatography (Scheme 2).




**Reagents**: i, $N_2CHCO_2Et$, LDA, THF -78°C; ii, benzene reflux 48h; iii, $PhCH_2OH$, DMAP, toluene reflux 48h; iv, $H_2$- Pd/C 10%; v, DME reflux 1.5h

**Scheme 2**

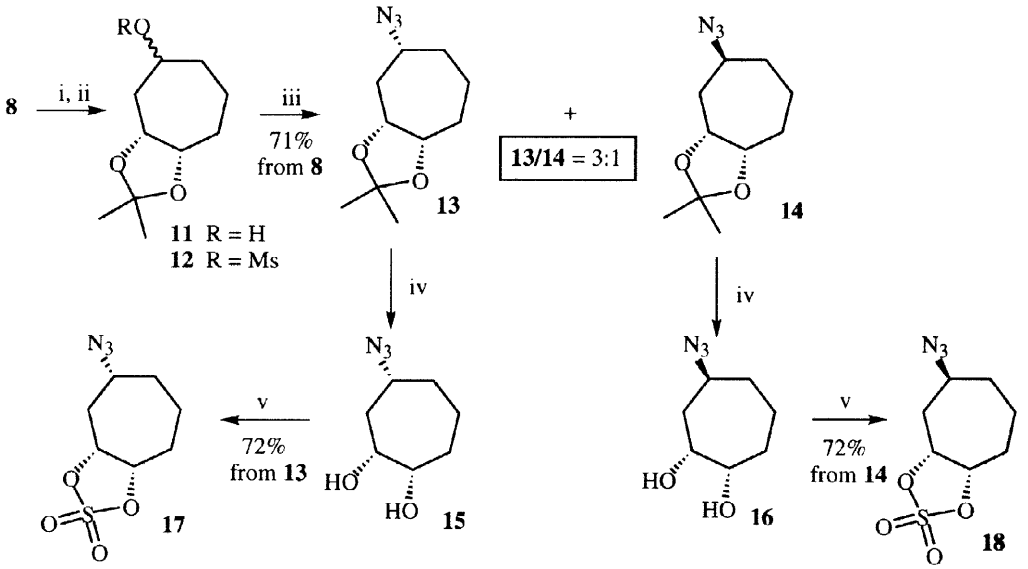
The lack of optical activity and a distinctive pattern of signals in the $^1H$ and $^{13}C$ NMR spectra for the *meso* compound **9** allowed us to identify the required isomer **8**.




**Scheme 3**

At this point, being unable to accumulate substantial amounts of the required isomer **8**, we were forced to look at a suitable method to overcome this hurdle. We discovered that submitting the mixture of the isomeric ethyl β-ketoesters **4** and **5** to the action of Bakers' Yeast (B.Y.) under classical experimental conditions,[15,16] only the minor isomer **5** was reduced at the β carbon. Thus, filtering the suspension after 24 hours a mixture of the major isomer **4** and the β-hydroxy ester **10** was obtained and easily separated by chromatography.

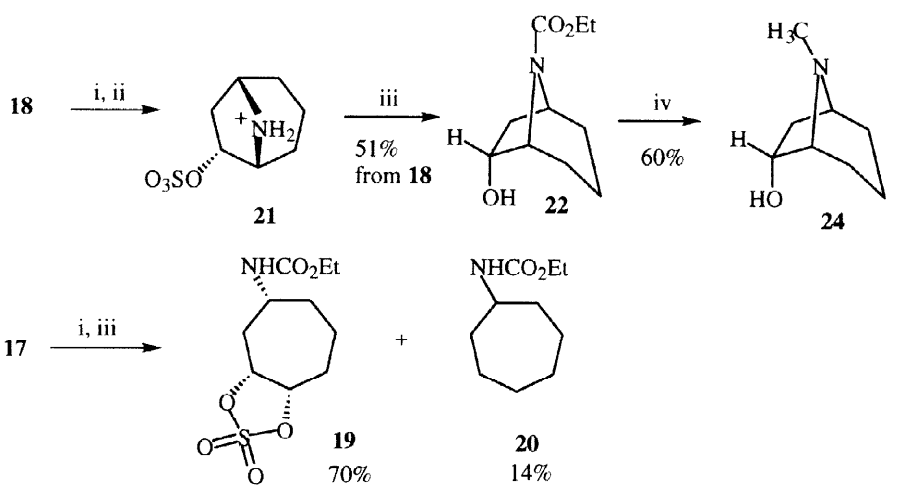
Interestingly, the B.Y. reduction of the β-ketoester **5** proceeded in a diastereoselective manner as indicated by $^1H$ and $^{13}C$ NMR spectra of the resulting β-hydroxyester **10**. We have tentatively assigned the stereochemistry depicted in the Scheme 3 on the basis of the stereochemical outcome of B.Y. reduction of analogous cyclic β-ketoesters.[17] The transformation of the ethyl β-ketoester **4** into the desired cycloheptanone derivative **8** was subsequently accomplished by dimethylaminopyridine-catalyzed transesterification[18] into the corresponding benzyl ester **6** followed by decarbalkoxylation *via* a two step sequence involving catalytic hydrogenation and heating or directly by heating a dimethoxyethane solution in presence of ammonium formate and Pd/C 10%. Thus, the combined action of B.Y. and hydrogenolysis served to overcome the problem caused by the lack of regioselectivity in the homologation step, allowing us to accumulate a substantial amount of the required chiron **8** to further proceed our synthetic plan.




**Reagents**: i, $NaBH_4$ r.t.; ii, MsCl, $Et_3N$, $CH_2Cl_2$ 0°C; iii, $NaN_3$, DMF, 80°C 6h; iv, MeOH, HCl 5% r.t.; v, $SOCl_2$, $Et_3N$, $CH_2Cl_2$ then $RuCl_3$-$NaIO_4$, $CCl_4$-$CH_3CN$-$H_2O$, 1h.

**Scheme 4**

The stage was set to test the feasibility of the key intramolecular transannular cyclization to build up the tropane skeleton. Following the synthetic route already explored in our approach to (-)-epibatidine,[3] we needed to transform cycloheptanone **8** into azidosulfate **18**. Reduction of the keto group in **8** with $NaBH_4$ furnished an unseparable mixture of cycloheptanols **11** which were transformed into the corresponding methanesulfonyl esters **12** and submitted to azide displacement to produce a separable 3:1 mixture of isomers **13** and **14** (Scheme 4). Their stereochemistry will be assigned at a later stage in the synthesis. Acid-promoted hydrolytic removal of the isopropylidene unit from the separated isomers produced the corresponding *cis* diols **15** and **16** which were subsequently transformed into the azido cyclic sulfates **17** and **18** applying the original protocol developed by Sharpless.[19]

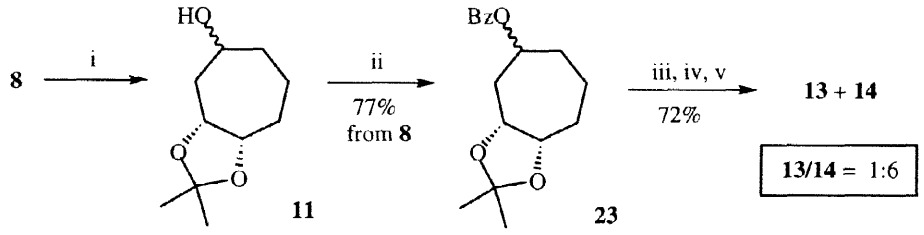



**Reagents**: i, $H_2$ 40 psi, Pd/C 10%, THF-$H_2O$; ii, dioxane, $H_2SO_4$, $H_2O$ 60°C 1h; iii, $ClCO_2Et$, $K_2CO_3$, r.t. 5h; iv, $LiAlH_4$, THF reflux 1h.

**Scheme 5**

These compounds showed a different chemical behaviour in the hydrogenation step: while the minor isomer **18** underwent the reduction of the azido group to the corresponding amino group which gave rise to

the desired internal displacement reaction with the formation of the inner salt **21**, the same process applied to predominant isomer **17** simply gave rise to the corresponding amine. In the latter case, treatment of the crude reaction mixture with ethylchloroformate to obtain less polar compounds, produced the expected N-protected cyclic sulfate **19** together with a small amount of the *N*-ethoxycarbonyl cycloheptylamine **20**. These results provide evidence for a *cis* relationship between the azido and the cyclic sulfate groups in **17**, being *trans* in the case of the minor isomer **18**. Having obtained the planned conversion of (-)-quinic acid into the tropane skeleton, our efforts were subsequently directed to an implementation of the strategy (Scheme 6). To this end, we firstly replaced $NaBH_4$ for the more hindered $LiAlH(O^tBut)_3$ as hydride donor in the reduction of the carbonyl group of **8**, then submitting the crude reaction mixture of secondary alcohols **11** to Mitsunobu conditions[20] making use of benzoic acid as nucleophile in order to achieve inversion of configuration at the newly created stereocenter. Methanolysis of the benzoate group of the derived mixture **23**, followed by esterification with methansulfonylchloride and $NaN_3$ displacement led us to obtain a 6:1 mixture of the azidoderivatives **14** and **13**. The better diastereoselectivity in the reduction of the carbonyl group of **8** accounted for the more favourable ratio compared with the previously obtained 1:3.




**Reagents**: i, $LiAl(OtBu)_3H$, THF -78°C; ii, $Ph_3P$, PhCOOH, DEAD, THF 0°C 1h; iii, $K_2CO_3$,MeOH 40°C 3h; iv, MsCl, $Et_3N$, $CH_2Cl_2$ 0°C; v, $NaN_3$, DMF, 80°C 6h. **Scheme 6**

The stereochemistry of the predominant diastereomer **14** is suitable for the successful intramolecular ring closure, thus allowing us to obtain an increased amount of the alcohol **22** required for the preparation of the known tropan-6α-ol **24** in optically active form through reduction with an excess of $LiAlH_4$ .The spectral properties of **24** match those recorded by Malpass *et al.*[21] for the racemic compound.

In conclusion, we have demonstrated the possibility to obtain an optically pure tropane 6α-hydroxy-substituted derivative employing (-)-quinic acid as the chiral source through a methodology which could in principle be applied to the preparation of more complex structures having this moiety as a key structural motif. Moreover, these results demonstrate once more the versatility of (-)-quinic acid as a synthon for the construction of optically pure medium size cyclic nitrogen-containing chirons.

## Experimental section

**General remarks.** Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Infrared (IR) spectra were taken on a FT-IR Paragon 500 spectrometer. Nuclear magnetic resonance ($^1H$ NMR and $^{13}C$ NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted and chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard. Coupling constants are given in Hertz. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40-60 °C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230-400 mesh). All reactions were carried out under $N_2$ or Ar atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

**(4*R*,5*S*)-2-Oxo-4,5-*O*-isopropylidene-cycloheptane-1-carboxylic acid ethyl ester (4) and (5*S*,6*R*)-2-Oxo-5,6-*O*-isopropylidene-cycloheptane-1-carboxylic acid ethyl ester (5).** To a cooled (-78°C) solution of **2**[10] (2g, 11.76mmol) and ethyl diazoacetate (1.3ml, 12.94mmol) in dry THF (35ml) a -78°C solution of LDA [prepared from 1.6M BuLi (8ml, 12.94mmol) and diisopropylamine (1.8ml, 12.94mmol)] in THF (20ml) was added dropwise *via* cannula (using $N_2$ positive pressure). The solution was stirred at the same temperature for 1.5h, poured into a cooled (-78°C) solution of glacial acetic acid (1.1ml) in diethyl ether (20ml), washed with water and brine. The combined organic extracts were dried and evaporated to give **3** as an orange oil which was dissolved in dry benzene (35ml). The solution was heated at reflux for 48h, the solvent stripped off and the residue subjected to flash chromatography (eluent: EtOAc: light petroleum 1.5: 8.5, then 1:4) to provide the mixture of **4** and **5** (1.7g, 57%) as a yellow oil. IR (neat): 1744, 1712, 1644, 1613 $cm^{-1}$.

**(3*R*,4*S*)-3,4-*O*-Isopropylidene-cycloheptan-1-one (8) and *meso*-4,5-*O*-Isopropylidene-cycloheptan-1-one (9).** To a solution of **4** and **5** (0.6g, 2.34mmol) in dry toluene (30ml) were added benzyl alcohol (0.5ml, 4.8mmol) and DMAP (28mg, 0.2mmol) and the resulting mixture refluxed for 48h. Removal of the solvent furnished the crude mixture of **6** and **7** (0.8g) as a brown oil which was dissolved in EtOAc (10ml) and hydrogenated in a Parr apparatus for 1.5h in the presence of Pd/C 10% (0.1g). Filtration through Celite and evaporation of the solvent provided a solid residue which was dissolved in 1,2-dimethoxyethane (10ml) and heated at reflux for 1.5h. Removal of the solvent *in vacuo* was followed by flash chromatography (eluent: EtOAc: light petroleum 3:7) of the residue to furnish the mixture of **8** and **9** (0.26g, overall yield 60%), which could be partially separated to yield analytical samples for spectroscopic characterization. **8**: colourless oil, $[\alpha]_D^{25}$-28.8 (c 1.1, $CHCl_3$); IR (neat): 1704 $cm^{-1}$; $^1H$ NMR: δ 1.34 (s, 3H, Me), 1.47 (s, 3H, Me), 1.5-1.7 (m, 1H), 1.9-2.2 (m, 3H), 2.2-2.7 (m, 3H), 2.9 (m, 1H), 4.3 (m, 2H, 2 CHOCMe$_2$); $^{13}C$ NMR: δ 18.1, 24.5, 27.2, 28.7, 44.8, 45.1, 73.2, 76.9, 107.9, 208.9. Anal. Calcd. for $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75. Found: C, 65.23; H, 8.70. **9**: colourless oil, IR (neat): 2983, 2935, 1710 $cm^{-1}$; $^1H$ NMR: δ 1.39 (s, 3H, Me), 1.51 (s, 3H, Me), 1.3-2.2 (m, 4H, 2 CH$_2$CHO-), 2.33 (ddd, 2H, J=2.4, 10, 14.77, 2 CH$_a$H$_b$-C=O), 2.78 (ddd, 2H, J=2.7, 10, 14.77, 2 CH$_a$H$_b$-C=O), 4.4 (m, 2H, 2 CHOCMe$_2$); $^{13}C$ NMR: δ 24.8, 27.2, 37.7, 76.1, 107.4, 211.5. Anal. Calcd. for $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75. Found: C, 65.21; H, 8.73.

**(1*R*,2*S*,5*S*,6*R*)-2-Hydroxy-5,6-*O*-isopropylidene-cycloheptane-1-carboxylic acid ethyl ester (10).** A mixture of **4** and **5** (1g, 3.9mmol) was added to a suspension of Baker's yeast (8g) and glucose (4g) in distilled water (80ml) and the mixture rapidly stirred at 30°C for 24h. After filtration through Celite, the filtrate was extracted with EtOAc (3x50ml). The dried organic extracts were concentrated and the residue purified by column chromatography (eluent: EtOAc: light petroleum 1:9, then 1:4) to give **4** (0.55g) and **10** (0.25g). **4**, yellow oil: $^1H$ NMR: δ 1.28 (m, 6H, OCH$_2$CH$_3$, Me), 1.35 (s, 3H, Me), 1.6-3.1 (m, 6H), 3.4-3.6 (2dd, 1H, J=8.5, 5.7 and J=7.1, 5.7), 4.1-4.4 (m, 4H, OCH$_2$CH$_3$, 2 CHOCMe$_2$), 12.7 (s, 1H). Anal. Calcd. for $C_{13}H_{20}O_5$ requires C, 60.91; H, 7.87. Found: C, 60.89; H, 7.90. **10**, white solid, m.p. 61°C, $[\alpha]_D^{25}$+57.4 (c 1.13, $CHCl_3$); IR (KBr): 3494, 1731 $cm^{-1}$; $^1H$ NMR: δ 1.27 (t, 3H, J=7.1, OCH$_2$CH$_3$), 1.36 (s, 3H, Me), 1.5 (s, 3H, Me), 1.7-2.1 (m, 5H), 2.3 (m, 1H), 2.9 (m, 1H, CHCO$_2$Et), 3.2 (bs, 1H, OH), 4.16 (q, 2H, J=7.1, OCH$_2$CH$_3$), 4.2 (m, 1H, CHOH), 4.4 (m, 2H, 2CHOCMe$_2$); $^{13}C$ NMR: δ 14.1, 23.1, 23.6, 26.0, 26.3, 27.6, 44.0, 60.8, 67.9, 74.9, 76.3, 106.3, 176.3. Anal. Calcd. for $C_{13}H_{22}O_5$ requires C, 60.45; H, 8.58. Found: C, 60.48; H, 8.55.

**(1*S*,3*R*,4*S*)-1-*O*-Methylsulfonyl-3,4-*O*-isopropylidene-cycloheptane and (1*R*,3*R*,4*S*)-1-*O*-Methylsulfonyl-3,4-*O*-isopropylidene-cycloheptane (12).** To a stirred solution of **8** (0.2g, 1.1mmol) in methanol (10ml) was added sodium borohydride (42mg, 1.1 mmol) in one portion at room temperature. After the reaction was complete (10min), the solvent was removed under reduced pressure and the residue was partitioned between water and ether. The organic extracts were dried and evaporated to give **11** as an oil. The crude **11** was dissolved in $CH_2Cl_2$ (3ml), ice-cooled (0°C) and treated with triethylamine (0.19ml, 1.32mmol) and methanesulfonyl chloride (0.11ml, 1.32mmol) and the mixture stirred at room temperature for 1h. Brine (10ml) was added, the organic phase separated, dried and evaporated to give **12** as a colorless oil which was used in the next step without further purification.

**(1*R*,3*R*,4*S*)-1-Azido-3,4-*O*-isopropylidene-cycloheptane (13) and (1*S*,3*R*,4*S*)-1-Azido-3,4-*O*-isopropylidene-cycloheptane (14).** To a solution of **12** (0.27g, 1.02mmol) in DMF (5ml), $NaN_3$ (0.33g, 5mmol) was added and the mixture heated at 80°C for 6h. The solvent was removed, the residue diluted with EtOAc (10ml) and the solution washed with brine (2x10ml). The combined organic extracts were dried, evaporated and the residue purified by flash chromatography (eluent: ether: light petroleum 0.5:9.5) to give **13** (0.12g) and **14** (40mg) as yellow oils (overall yield 71%): **13**: $[\alpha]_D^{25}$+2.5 (c 1.02, $CHCl_3$); IR (neat): 2090 $cm^{-1}$; $^1H$ NMR: δ 1.2-1.7 (9H: m, 3H and 2s, 6H, 2 Me), 1.8-2.2 (m, 5H), 3.2 (m, 1H, CHN$_3$), 4.2 (m, 2H, CHCOMe$_2$). Anal. Calcd. for $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.11; N, 19.89. Found: C, 56.88; H, 8.08; N, 19.88.**14**: $[\alpha]_D^{25}$ +49.5 (c 0.96, $CHCl_3$). IR (neat): 2092 $cm^{-1}$; $^1H$ NMR: δ 1.34 (s, 3H, Me), 1.47 (s, 3H, Me), 1.5-1.8 (m, 4H), 1.8-2.0 (m, 3H), 2.1 (m, 1H), 3.8 (m, 1H, CHN$_3$), 4.4 (m, 2H, 2 CHOCMe$_2$). Anal. Calcd. for $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.11; N, 19.89. Found: C, 56.80; H, 8.13; N, 19.90.

**(1*R*,3*R*,4*S*)-1-Azido-3,4-*O*-sulfonyl-cycloheptane (17) and (1*S*,3*R*,4*S*)-1-Azido-3,4-*O*-sulfonyl-cycloheptane (18).** A solution of **13** (0.36g, 1.7mmol) in MeOH (5ml) was stirred at room temperature for 2h in the presence of 5% HCl (5ml). The solvents were evaporated, the residue dissolved in $CH_2Cl_2$ (16ml) and the solution cooled at 0°C. Triethylamine (0.95ml, 6.8mmol) and $SOCl_2$ (0.43ml, 5.9mmol) were successively added and, after being stirred at the same temperature for 10min, the reaction mixture was diluted with ether (25ml) and washed with ice-water (20ml). The separated organic phase was dried, evaporated and the residue dissolved in 1:1 mixture of $CCl_4$ (11ml) and $CH_3CN$ (11ml). Water (17ml) was added and the ice-cooled (0°C) solution was treated with a catalytic amount of $RuCl_3$ (15mg) and $NaIO_4$ (0.53g, 2.47mmol) and kept at room temperature for 1h before diluting with ether (20ml). The phases were separated, the aqueous phase extracted with ether (3x10ml), the organics dried and the solvent removed *in vacuo*. The residue was subjected to flash chromatography (eluent: EtOAc: light petroleum 1:4) to afford **17** (0.28g, 72%) as a yellow oil, $[\alpha]_D^{25}$+16.63 (c 1.45, $CHCl_3$); IR (neat): 2098 $cm^{-1}$; $^1H$ NMR: δ 1.26 (m, 1H), 1.54 (m, 1H), 1.7-2.5 (m, 6H), 3.36 (tt, 1H, J=3, 10.4, C<u>H</u>N$_3$), 5.0 (m, 2H, 2 C<u>H</u>OS); $^{13}C$: δ 19.1, 28.2, 35, 57.6, 80.8, 83. Anal. Calcd. for $C_7H_{11}N_3O_4S$ requires C, 36.05; H, 4.75; N, 18.02. Found: C, 36.03; H, 4.77; N, 18.98.Submitting **14** to the same protocol, **18** was obtained as a yellow oil (73%), $[\alpha]_D^{25}$+55.5 (c 1.22, $CHCl_3$). IR (neat): 2098 $cm^{-1}$; $^1H$ NMR: δ 1.5-2.5 (m, 8H), 4.0 (m, 1H, C<u>H</u>N$_3$), 5.0 (td, 1H, J=7.1, 4.6, C<u>H</u>OS), 5.2 (td, 1H, J=7.1, 4.2, C<u>H</u>OS). Anal. Calcd. for $C_7H_{11}N_3O_4S$ requires C, 36.05; H, 4.75; N, 18.02. Found: C, 36.08; H, 4.73; N, 18.01.

**(1*R*,3*R*,4*S*)-1-*N*-Ethoxycarbonylamino-3,4-*O*-sulfonyl-cycloheptane (19) and *N*-ethoxycarbonylamino-cycloheptane (20).** To a solution of **17** (0.11g, 0.47mmol) in 1:1 THF/$H_2O$ (10ml), 10% Pd/C (20mg) was added and the mixture hydrogenated in a Parr apparatus at 40psi for 2h. The catalyst was filtered through Celite and the solvent evaporated to give a solid residue which was immediately dissolved in MeOH (6ml). Ethyl chloroformate (0.18ml, 1.9mmol) and $K_2CO_3$ (0.34g, 2.82mmol) were successively added and the mixture was allowed to stand at room temperature for 5h. Most of the solvent was stripped off and the reaction mixture extracted with EtOAc (2x10ml), dried and concentrated. The residue was purified by flash chromatography (eluent: EtOAc: light petroleum 1:4, then 1:1) to yield **19** (91mg, 70%) and **20** (12mg, 14%) as colourless oils: **19**: $[\alpha]_D^{25}$+34.8 (c 3.08, $CHCl_3$); IR (neat): 3409, 3323, 1697 $cm^{-1}$; $^1H$ NMR: δ 1.1-1.4 (m, 4H), 1.8-2.4 (m, 7H), 3.4 (m, 1H, C<u>H</u>N), 4.0 (m, 2H, OC<u>H</u>$_2$CH$_3$), 4.7 (bd, 1H, N<u>H</u>), 4.9-5.2 (m, 2H, 2 C<u>H</u>OS); $^{13}C$: δ 14.6, 19.7, 28.4, 36.4, 36.5, 48.4, 61.1, 81.5, 83.3, 155.5. Anal. Calcd. for $C_{10}H_{17}NO_6S$ requires C, 43.00; H, 6.13; N, 5.01. Found: C, 42.98; H, 6.14; N, 5.02; **20**: IR (neat): 3327, 1693 $cm^{-1}$; $^1H$ NMR: δ 1.23 (t, 3H, J=7.1, OCH$_2$C<u>H</u>$_3$), 1.4-1.8 (m, 10H), 1.9-2.1 (m, 2H), 3.7 (m, 1H, C<u>H</u>N), 4.1 (q, 2H, J=7.1, OC<u>H</u>$_2$CH$_3$), 4.6 (b, 1H, N<u>H</u>); $^{13}C$: δ 14.7, 23.9, 28.1, 35.4, 52, 60.5, 156. Anal. Calcd. for $C_{10}H_{19}NO_2$ requires C, 64.83; H, 10.34; N, 7.56. Found: C, 64.85; H, 10.33; N, 7.57.

**(1*S*,5*R*,6*R*)-*N*-Ethoxycarbonyl-6-hydroxy-8-azabicyclo[3.2.1]octane (22).** A solution of **18** (0.16g, 0.68mmol) in 1:1 THF/$H_2O$ (15ml) was hydrogenated in a Parr apparatus at 40psi for 2h, in the presence of 10% Pd/C (30mg). Filtration of the catalyst through Celite and solvent evaporation gave **21**, $^{13}C$ ($CD_3OD$): δ 16.8, 24.7, 29.5, 34.0, 56.2, 57.8, 75.3, which was dissolved in 1,4-dioxane (8ml) with one drop of concentrated $H_2SO_4$ and two drops of water added and the mixture was heated at 60°C for 1h. The solvent was evaporated and the residue was dissolved in MeOH (5ml). Ethyl chloroformate (0.25ml, 2.6mmol) and $K_2CO_3$ (0.56g, 4mmol) were successively added and the mixture stirred at room temperature for 5h. Most of the solvent was evaporated and the residue extracted with EtOAc (2x10ml), dried and concentrated. The residue was purified by flash chromatography (eluent: EtOAc: light petroleum 1:1) to yield **22** (67mg, 51%) as a colourless oil: $[\alpha]_D^{25}$+5.4 (c 1.28, $CHCl_3$); IR (neat): 3418, 1667 $cm^{-1}$; $^1H$ NMR ($CDCl_3/D_2O$): δ 1.2 (t, 3H, J=7, OCH$_2$C<u>H</u>$_3$), 1.4-2.2 (m, 7H), 2.5 (m, 1H), 4.0-4.3 (m, 4H, OC<u>H</u>$_2$CH$_3$ and 2 C<u>H</u>N), 4.5 (m, 1H, C<u>H</u>OH). $^{13}C$: δ 14.8, 17.1, 24.6 and 25.2, 29.8 and 30.5, 36.9 and 37.4, 53.3, 56.5, 60.9, 70.9 and 71.5, 154. Anal. Calcd. for $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03. Found: C, 60.26; H, 8.61; N, 7.04.

**(1*S*,5*R*,6*R*)-*N*-Methyl-6-hydroxy-8-azabicyclo[3.2.1]octane (Tropan-6α-ol) (24).** A solution of **22** (26mg, 0.13mmol) in THF (2ml) was added dropwise to a cooled (0°C) slurry of lithium aluminium hydride (15mg, 0.4mmol) in THF (2ml), and the mixture was heated at reflux for 1h. Ether (5ml) and water (0.1ml) were added, the inorganic salts filtered through Celite and the solvent removed in vacuo. The residue was purified by flash chromatography (eluent: triethylamine: MeOH: EtOAc 1:1:3) to afford **24** (11mg, 60%), $[\alpha]_D^{25}$-4 (c 0.57, $CHCl_3$), whose physical and spectroscopic properties were identical in all respects to that reported by Malpass *et al.*[21] for the racemic compound.

**(1*S*,3*R*,4*S*)-3,4-*O*-Isopropylidene-cycloheptan-1-ol and (1*R*,3*R*,4*S*)-3,4-*O*-Isopropylidene-cycloheptan-1-ol (11).** A solution of **8** (90mg, 0.49mmol) in THF (5ml) was added dropwise to a cooled (-78°C) suspension of $LiAl(O^tBu)_3H$ (0.15g, 0.6mmol) in THF (20ml). After being stirred for 1h at the same temperature, the mixture was treated with aqueous $NH_4Cl$ (5ml) and extracted with EtOAc (3x10ml). The dried extracts were evaporated to give quantitatively **11** as an oil which was used in the following step without purification.

**(1*S*,3*R*,4*S*)-1-Benzoyloxy-3,4-*O*-isopropylidene-cycloheptane and (1*R*,3*R*,4*S*)-1-Benzoyloxy-3,4-*O*-isopropylidene-cycloheptane (23).** To an ice-cooled (0°C) solution of **11**

(0.25g, 1.34mmol), $Ph_3P$ (0.53g, 2mmol) and benzoic acid (0.25g, 2mmol) in THF (13ml), DEAD (0.32ml, 2mmol) was added dropwise and the reaction mixture was stirred at the same temperature for 1h. The solvent was evaporated and the residue purified by flash chromatography (eluent: EtOAc: light petroleum 1:9) to give **23** (0.3g, 77%) as an oil, IR (neat): 1715 $cm^{-1}$. Methanolysis of the benzoate group of **23** at 40°C for 3h in the presence of saturated $K_2CO_3$ solution, followed by esterification with methanesulfonyl chloride and $NaN_3$ displacement according to the protocol described above, furnished a 1:6 mixture of **13** and **14**, which were isolated by flash chromatography.

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