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A Unified Asymmetric Approach to Substituted Hexahydroazepine and 7-Azabicyclo[2.2.1]heptane Ring Systems from D(-)-Quinic acid: Application to The Formal Syntheses of (-)-Balanol and (-)-Epibatidine.

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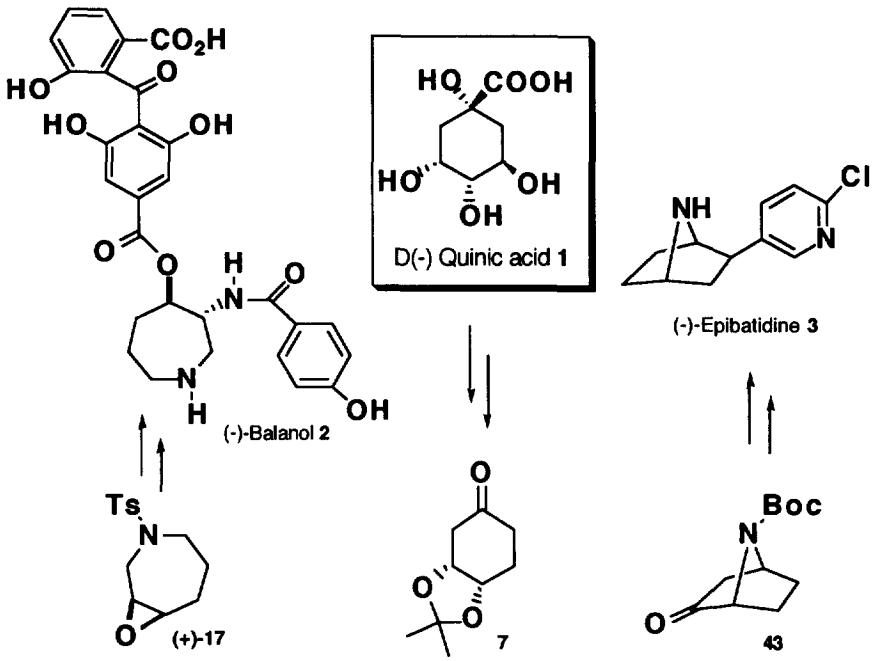
Abstract: 3,4-*O*-Isopropylidene-3(*R*),4(*S*)-dihydroxycyclohexanone **7**, a chiron easily prepared through a five step sequence from D(-)-quinic acid **1**, has been efficiently utilized as the starting building block for the enantioselective syntheses of *(3R,4S)-N-p*-toluenesulfonyl-3,4-epoxy-hexahydroazepine **17** and *(1R,4S)-N-tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one **43**, advanced intermediates already taken to (-)-balanol and (-)-epibatidine respectively. While the nitrogen atom ring-insertion *via* Beckmann rearrangement was the key step for the construction of the hexahydroazepine ring of **17**, a regio- and stereospecific intramolecular nucleophilic ring opening of an intermediate cyclic sulfate featured the approach to the substituted 7-azabicyclo[2.2.1]heptane nucleus of **43**.

The development of methods for the asymmetric synthesis of biologically active compounds continue to be an area of intense research primarily due to the generally observed enantiospecificity of the biological responses, which compel chemists to prepare both enantiomers of a molecular target for the subsequent pharmacological tests. In planning asymmetric synthesis, the use of naturally occurring substances belonging to the "chiral pool" is an effective tool to gain access to one or both enantiomers of a chiral target.

Herein we describe our own efforts in devising convenient synthetic entries to nitrogen containing chiral building blocks such as the 7-azabicyclo[2.2.1]heptane ring system **43** and to the hexahydroazepine fragment (+)**17**, which paved the way to a new enantioselective formal synthesis of (-)-balanol **2** and (-)-epibatidine **3**, two popular targets for synthesis owing to the structural novelty and the relevant pharmacological profile.

Interestingly, as retrosynthetically indicated in Scheme 1, both syntheses rely on the use of D(-)-quinic acid **1**, a commercially available inexpensive plant metabolite, as the common chiral educt. This compound represents an attractive starting point widely utilized for asymmetric multistep syntheses of naturally occurring substances and related compounds.[1]

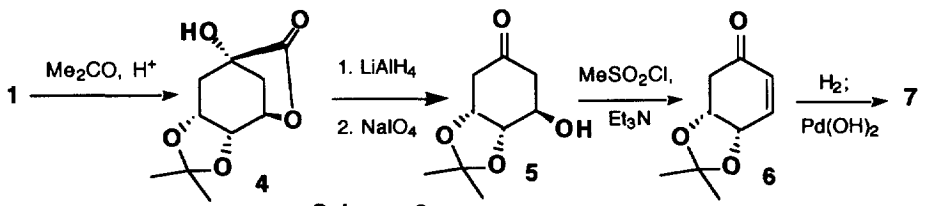
However, most of the applications have been to the synthesis of polyfunctionalized cyclohexane and cyclopentane ring systems or open chain synthons while less attention has been devoted to the preparation of heterocyclic structures.



Scheme 1

Our continuous synthetic interest in the field of biologically active compounds prompted us to investigate the opportunity of producing nitrogen containing chirons taking advantage of the five-step sequence depicted in Scheme 2, which allowed the separation of the reactivity of the functional groups present in quinic acid furnishing multigram quantities of 7.[2,3]

Thus, the acid-catalyzed treatment of **1** at room temperature with acetone proceeded smoothly to produce the crystalline γ-lactone **4** through the protection of the C-3 and C-4 hydroxyl groups in form of isopropylideneketal, while a concomitant lactonization takes place between the carboxyl group at C-1 and the hydroxyl at C-5. The γ-lactone moiety was efficiently reduced by means of lithium aluminum hydride to produce the 1,2-diol functionality at C-1 which acts as a synthon for a carbonyl group, easily generated through sodium metaperiodate oxidation to afford the β-hydroxy cyclohexanone **5**.



Scheme 2

Methanesulfonyl chloride/triethylamine or acetic anhydride/diisopropylethylamine[1] dehydration of the latter, most likely favoured by the boat conformation of the cyclohexane ring due to the presence of the isopropylidene

ketal ring system, easily occurred to produce the cyclohexenone derivative **6**, eventually converted to the key intermediate **7** by hydrogenation in the presence of $Pd(OH)_2$.

We selected the chiron **7**, still retaining two of the original stereogenic centers of quinic acid, as the common chiral starting point for a new enantioselective approach to both the key intermediates (+)-**17** and **43**, which have been already taken to (-)-balanol **2**[4,5] and (-)-epibatidine **3**[6,7] respectively. Therefore, their preparation represents a formal synthesis of both natural compounds.

Synthesis of chiral *N*-*p*-toluenesulfonyl-3,4-disubstituted hexahydroazepines.

(-)-Balanol **2** is an unusual metabolite produced by the fungus *Verticillum Balanoides* displaying remarkable inhibitory properties towards protein Kinase C.[8] The potential therapeutic usefulness of these enzyme inhibitors have stimulated the development of synthetic schemes to the natural compound, sufficiently flexible to gain access to congeners suitable for screening as new drugs against cancer and other diseases. A synthetic approach to balanol presents invariably two distinct synthetic challenges namely, the asymmetric synthesis of the central 3,4-disubstituted hexahydroazepine ring system and the construction of the fully functionalized benzophenone fragment connected to it through an ester linkage.

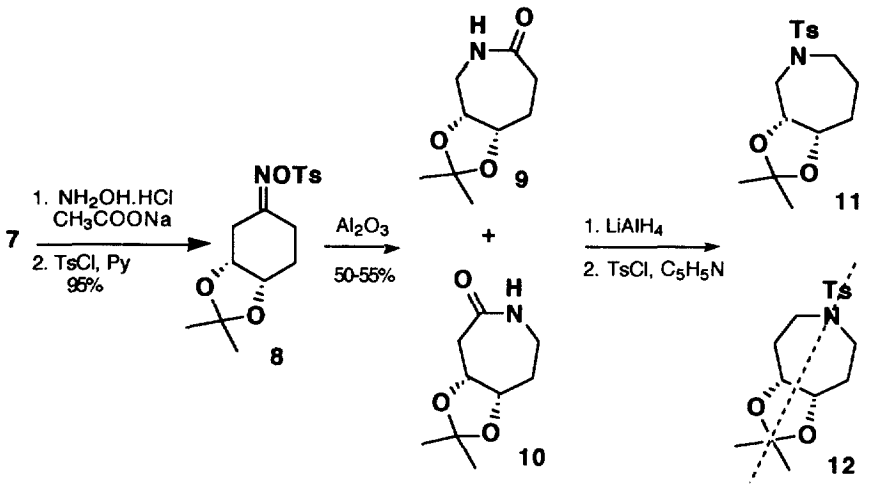
As a consequence, many efforts have been focused to the development of procedures for the preparation of suitably *N*-protected-3-amino-4-hydroxyhexahydroazepine derivatives in both racemic and optically active forms.[5] The reported asymmetric approaches utilize chiral starting materials obtained through Sharpless asymmetric *cis*-hydroxylation[9] and epoxidation[4] or by asymmetric epoxide ring opening reaction,[10] while enantioselective routes have been developed using readily available chiral materials such as D-serine,[11,12] D-isoascorbic acid[13] and D(-)-quinic acid.[14]

We planned to obtain chiral polyhydroxylated lactams including the targeted hexahydroazepine **11** in a completely enantiospecific way using the Beckmann rearrangement as a tool for the nitrogen incorporation.[15] Two main problems were inherent to the present approach: first, to keep the functionalities and the original stereogenic centers unaffected under the experimental conditions required to promote the rearrangement; second, a likely non regiospecific nitrogen atom incorporation could lead to the formation of isomeric mixture of lactams. As far as the first issue is concerned, many experimental protocols have been developed over the years, including neutral inducers; we found[14,15] it very convenient to employ basic alumina[16] to activate the required oxime derivatives to undergo Beckmann rearrangement.

Accordingly, the cyclohexanone derivative **7** was treated with hydroxylamine and then with *p*-toluenesulfonyl chloride to give almost quantitatively the corresponding mixture of the oxime sulfonates **8**, which were directly passed through a short alumina column eluting first with CH_2Cl_2 and then with methanol. By collecting the more polar fractions we were able to isolate a mixture of the lactams **9** and **10** in 50-55% overall yield. (Scheme 3)

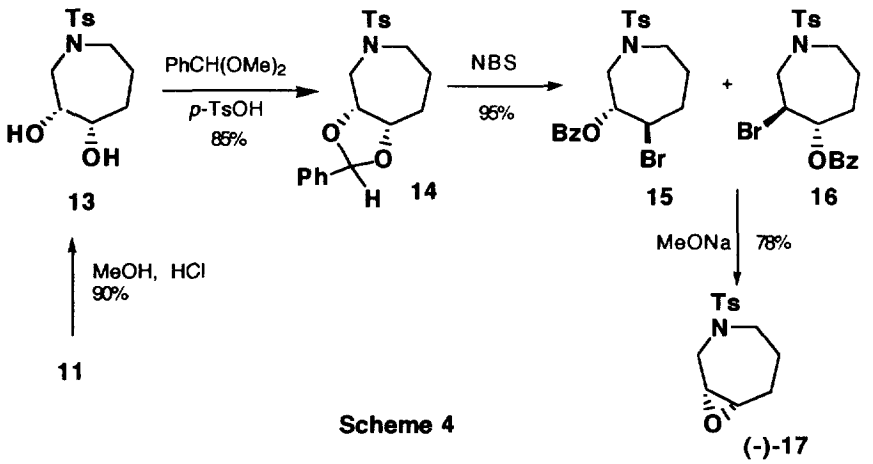
The Beckmann rearrangement proceeded smoothly but, as expected, not regiospecifically, under these mild conditions.

However, this drawback was partially mitigated in view of the easy separation of the pure lactam **9** by simple crystallization. Moreover, $LiAlH_4$ reduction of the mixture of **9** and **10**, followed by treatment with *p*-toluenesulfonyl chloride gave rise to a 4:1 mixture of *N*-tosyl hexahydroazepines **11** and **12** separable by flash chromatography.



Scheme 3

The *meso* structure **12** was easily determined on the basis of its spectral properties, thus allowing the unambiguous assignement of the structure **11** to the major isomer and, indirectly, those of the lactams **9** and **10**. Aqueous acid-promoted removal of the ketal protecting group from **11** furnished in high yield the crystalline chiral *cis* *N*-tosyl 3,4-dihydroxyhexahydroazepine **13**, which has been used as the starting material to prepare both the enantiomeric bicyclic epoxides (-)-**17** and (+)-**17**, the latter compound being already obtained with 90% e.e. by Tanner *et al.*[4] along a nice synthetic approach to balanol.



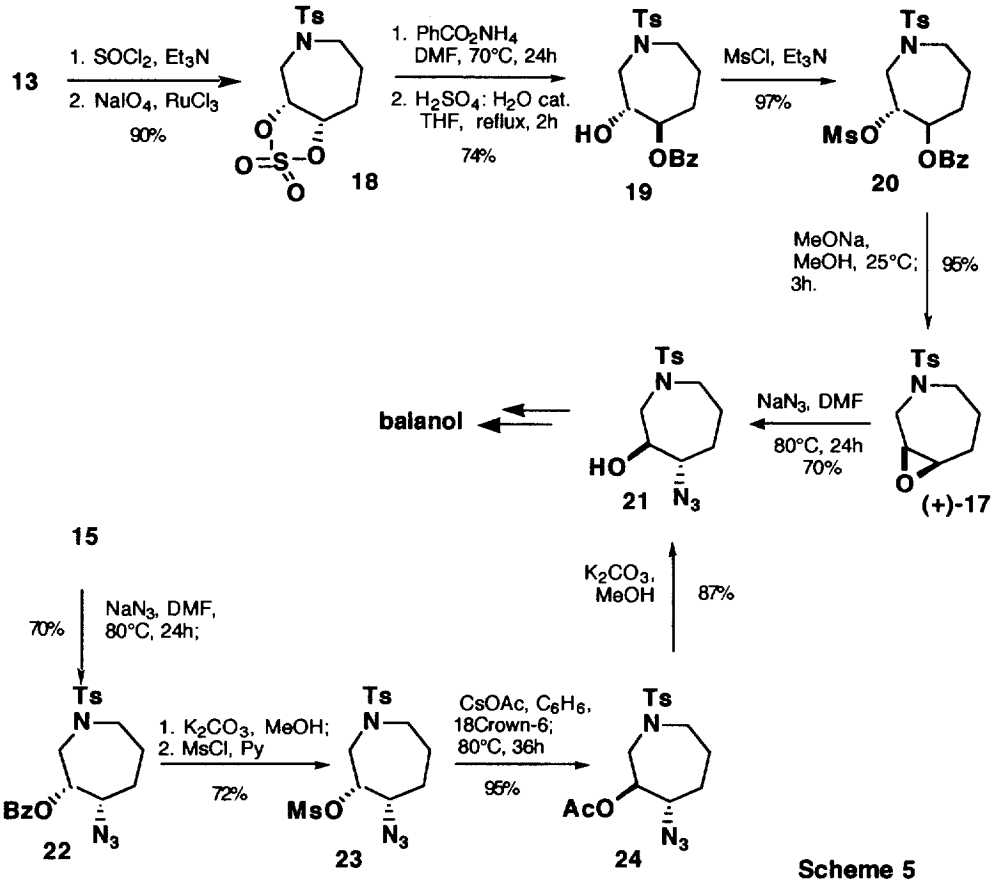
Scheme 4

Remarkably, our own approach opens a new way to both natural and non natural analogs. In details, acid-catalyzed reaction of **13** with benzaldehyde dimethylacetal at room temperature provided the benzylideneacetals **14** as a diastereomeric mixture at the newly introduced stereogenic centre of the acetal carbon.

According to the protocol originally introduced by Hanessian[17] on sugar derivatives, the crude mixture was exposed to *N*-bromosuccinimide to promote the benzylidene acetal ring opening. The process, although not

regiospecific, was completely stereospecific, affording in an essentially quantitative yield a 6:1 ratio of the isomeric *trans*-bromobenzoates **15** and **16**, both being suitable precursors exclusively for the bicyclic oxirane derivative (-)-**17**. (Scheme 4).

Removal of the benzoate ester by treatment of the crude mixture of **15** and **16** with sodium methoxide in methanol followed by intramolecular nucleophilic displacement of the bromine resulted in the clean formation of the crystalline epoxide (-)-**17**, isolated in high yield after chromatographic purification.



Scheme 5

Alternatively, treatment of the *cis-N*-tosyl-3,4-dihydroxyhexahydroazepine **13** with thionyl chloride afforded a diastereomeric mixture of cyclic sulfites which was directly transformed to the corresponding sulfate **18** by $NaIO_4$ oxidation in the presence of catalytic amounts of ruthenium trichloride according to the protocol developed by Sharpless[18] (Scheme 5).

Taking advantage of the epoxide-like reactivity of the cyclic sulfate moiety, we were able to convert **18** into the *trans*-dioxygenated hexahydroazepine derivative **19**, a convenient precursor of (+)-**17**, already taken to balanol,[5] using an excess of ammonium benzoate in refluxing DMF as the nucleophile. Subsequent acid-

catalyzed removal of sulfate group and esterification of the free hydroxyl with methanesulfonyl chloride afforded the chiral intermediate **20**, eventually transformed into (+)-**17** by treatment with sodium methoxide in methanol.

Remarkably, the stereospecific four step sequence involving the transformation of the diol **13** into both enantiomers of **17** could be accomplished in high overall yield without chromatographic purification, allowing us to consider this approach particularly attractive to gain access to the hexahydroazepine portion of both natural and unnatural balanol.

The oxirane ring opening of (+)-**17** by action of lithium azide to give regio- and stereospecifically the trans azidoalcohol **21** was already described by Tanner *et al.* on the way to balanol.[4,5] This intermediate could also be obtained through a rather tedious chemical elaboration of **15**, easily available in a pure state by simple fractional crystallization of the 6:1 mixture of the bromobenzoates originating by NBS reaction of **14**.

However, we embarked on this operation, which required the inversion of the configuration at both C-4 and C-3, with the aim to confirm the structures of the intermediates obtained in the pathway to both the enantiomers of **17**. Thus, nucleophilic displacement of the C-4 bromine cleanly took place by heating a DMF solution of **15** with an excess of sodium azide to provide the *cis*-bifunctionalized hexahydroazepine derivative **22**.

The inversion at C-3 required deprotection of the hydroxyl group by methanolysis, followed by transformation by standard methodology into the corresponding methanesulfonate derivative **23**, which was eventually submitted to the action of cesium acetate[19] in refluxing benzene in the presence of crown ether to give the corresponding acetyl derivative **24**. Its methanolysis furnished the crystalline 3(*S*)-hydroxy-4(*S*)-azido-*N*-*p*-toluenesulfonyl-hexahydroazepine **21**, identical in all respects to that described by Tanner *et al.*[4]

Enantioselective approach to (-)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one 43, an advanced intermediate in the synthesis of (-)-Epibatidine 3.

Epibatidine **3**, a structurally challenging and pharmacologically important simple alkaloid isolated in a trace amount by Daly *et al.*[20] in 1992 from Ecuadorian poison frog *Epipedobates tricolor*, has been the focus of intense synthetic interest over the past five years. The previous syntheses of **3** were reviewed in 1994 and since then several additional syntheses have appeared, indicating current widespread interest in this molecule.[21]

With limited functional groups, its skeletal structure provides an ideal model system for investigating general synthetic strategies for the construction of the rather uncommon 7-azanorbornane ring system to which a 3-chloropyridine substituent is attached in an *exo*-position.

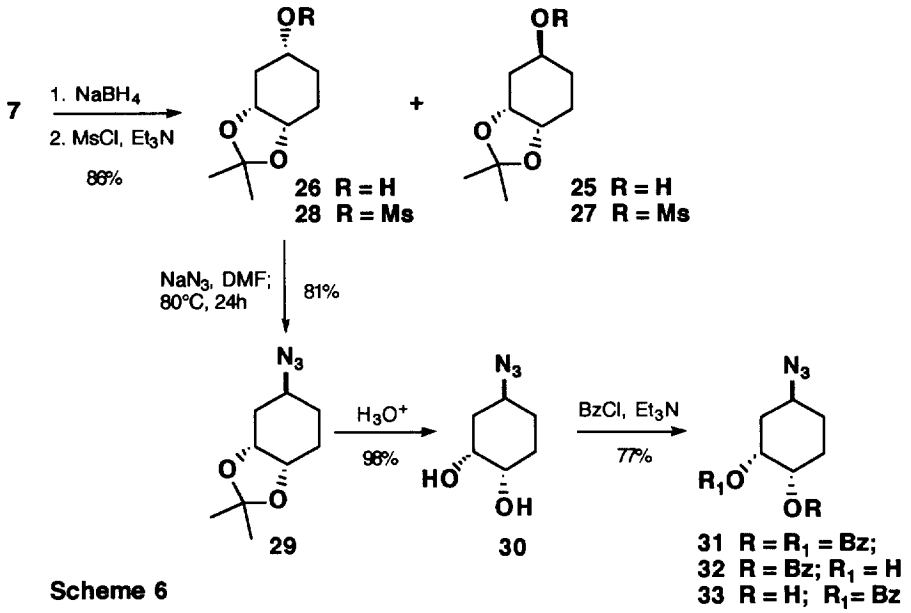
Despite its absolute configuration has been known since 1994[6] only two enantioselective approaches have been reported up to now, the first starting from L-glutamic acid,[22,23] the second one featuring a Pd-catalyzed desymmetrization of a *meso* intermediate as the key step.[24]

These approaches differ strategically not only in the creation of the required chirality, but especially for the timing of the union of the pyridyl nucleus to the aliphatic skeleton, which has been introduced after or before the nitrogen atom bridge construction respectively. The former strategy has been frequently used as a straightforward and versatile method for the construction of the basic skeleton of epibatidine.[6,23,25,26]

Thus, Fletcher *et al.*[6] in their relevant work in this area targeted (+)- and (-)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one, in turn obtained from earlier enantiomeric mixture resolution, and converted them to both epibatidine enantiomers, thus establishing the absolute configuration of the natural product.

We envisaged the building block **7**, easily available from D(-)-quinic acid, as the key chiral precursor for the preparation of a suitably *N*-protected-7-azabicyclo[2.2.1]heptan-2-one possessing the correct stereochemistry as required to obtain the natural alkaloid.

Conceptually, the nitrogen atom bridge in **43** could be installed through an intramolecular transannular cyclization of a suitably functionalized 1,4-*trans*-disubstituted-cyclohexane derivative.[27] With this in mind, the first challenge was the transformation of the starting ketone into the requisite cyclohexane ring system bearing the functional groups required to perform the key internal displacement reaction. In details, the elaboration of the carbonyl group of **7** into a nucleophilic nitrogen functionality able to react intramolecularly with an electrophilic center strategically located on the cyclohexane ring was undertaken as the first objective. (Scheme 6)



Scheme 6

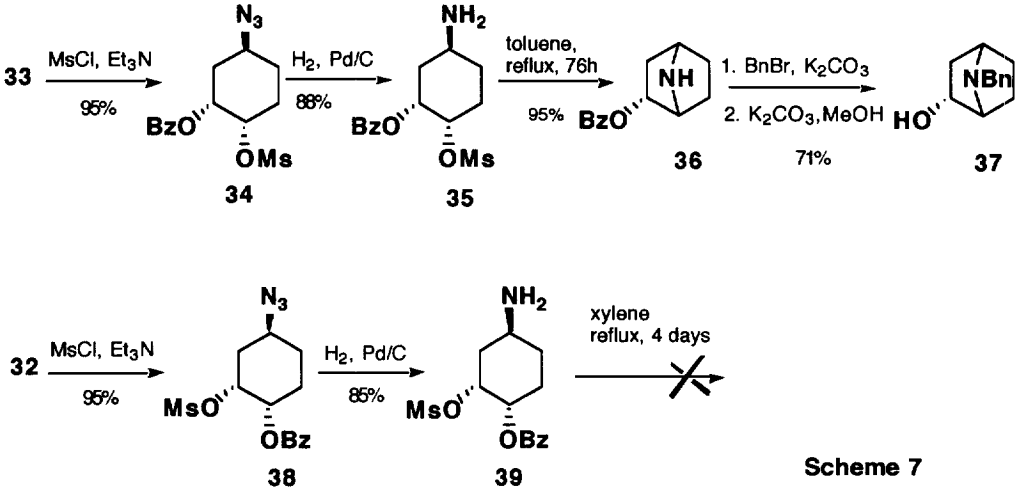
To pursuit our design, a stereoselective reduction of the carbonyl group to the corresponding α-oriented (*R*)-secondary alcohol was needed but could not be anticipated. Accordingly, $NaBH_4$ reduction of the keto group in **7** furnished in essentially quantitative yield an unseparable 1:11 mixture of the diastereomeric cyclohexanols **25** and **26**, the structures of which being tentatively attributed assuming a preferred β-hydride attack from *si* face, the less hindered side of the cyclohexanone **7**. The crude mixture was then submitted to the action of methansulfonyl chloride in the presence of triethylamine to produce the corresponding methansulfonyl esters **27** and **28** which could be separated by chromatography making it possible to further proceed utilizing a pure compound, namely the predominant isomer **28**.

The stage was set for the introduction of the nitrogen atom through the classical azide displacement which proceeded, as expected, stereospecifically by heating a solution of **28** in DMF with a fivefold excess of NaN_3 for 24h to afford the β-azido derivative **29** in 77% yield. At this point, the requisite arrangement of the cyclohexane ring for the transannular cyclization called for deprotection of the adjacent hydroxyl groups and, more importantly, for the separation of their reactivity.

The first issue could be easily achieved by exposure of **29** to aqueous acid which easily removed the acetal protecting group leading quantitatively to **30** as a low melting solid. However, attempts at differentiating the demasked *cis*-hydroxy groups through a regioselective formation of an ester derivative by reaction with acetyl or benzoyl chloride as well as methane- or *p*-toluenesulfonyl chloride led invariably to the formation of a mixture of

the regioisomeric mono- and diester derivatives. Initially, we exploited the transformation of the monobenzoylester **33**, isolated by column chromatography, into the chiral azabicycle **37** along the steps summarized in the Scheme 7.

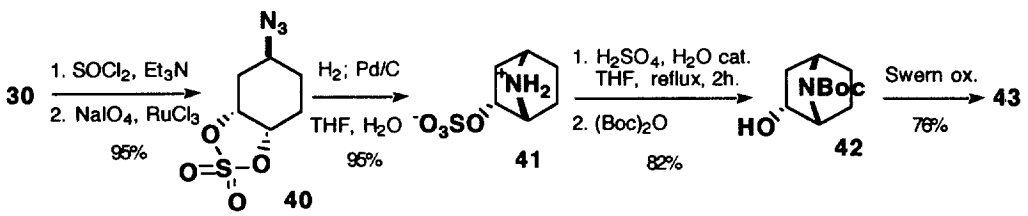
In details, when a toluene solution of **35**, in turn obtained by *O*-activation and azide reduction, was refluxed for 4 days the expected chiral azabicycle **36** could be obtained in good yield. Interestingly, the regioisomer **39**, derived from **32** through the same two-step procedure, slowly decomposed on heating in the same conditions, thus supporting the stereo- and regiochemical assignement given to the synthetic intermediates. Compound **36** was then easily *N*-alkylated by treatment with benzyl bromide and eventually *O*-deprotected by methanolysis to give levorotatory *N*-benzyl-2-*endo* hydroxy-7-azabicyclo[2.2.1]heptane **37** whose spectral properties match those recorded by Fletcher *et al.*[6] for the racemic compound.



Scheme 7

In order to improve our synthetic plan to chiral azabicycles which suffered the lack of regioselectivity in the monobenzoyl ester formation, we focused on a shorter route of chemical differentiation and turned our attention to the possibility of converting the *cis* vicinal hydroxyl groups of **30** into the corresponding cyclic sulfate **40** (Scheme 8).

We were confident that a complete regioselective internal displacement favouring a nucleophilic attack at C-4 *versus* C-3 could take place on this electrophilic moiety. To this end, we applied the standard two-step methodology[18] already described as for **18** to transform almost quantitatively the diol **30** into the cyclic sulfate **40**, which was then submitted to catalytic hydrogenation.



Scheme 8

Gratyfyingly, a smooth reduction of the azido group of **40** took place generating the corresponding amine which concomitantly gave rise to the planned internal displacement by attack to the opposite electrophilic carbon of the cyclohexane ring. Simple filtration of the catalyst and removal of the solvents allowed us to isolate in high yield the inner salt **41**: this transformation is noteworthy when compared with the very slow analogous internal displacement of the corresponding epoxide with the same nucleophilic counterpart. The crude aminoalcohol resulting from the removal of the sulfate group by acid-catalyzed hydrolysis was directly transformed by treatment with di-*tert*-butyl dicarbonate into the corresponding *N*-protected derivative **42**, which was eventually submitted to Swern oxidation to give the levorotatory *N*-Boc-7-azabicyclo[2.2.1]heptan-2-one **43** identical in all respects to that reported by Rapoport *et al.*[22,23]

Conclusion

The development of efficient processes for the enantioselective synthesis of both nitrogen containing seven-membered ring and 7-azabicyclo[2.2.1]heptane ring system derivatives extends the attractiveness of D(-)-quinic acid **1** as a chiral template for natural products synthesis.

Moreover, the chemistry described in this paper took enormous advantage of highly stereo- and regiospecific ring opening of cyclic sulfates by nucleophilic attack occurring both inter- and intramolecularly, stressing once more the versatility of this moiety in organic synthesis.

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Experimental.

General remarks. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared (IR) spectra were measured on a Perkin-Elmer Model 297. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted and peak positions are given in parts per millions downfield from a tetramethylsilane as an internal standard. Coupling constants are given in Hz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling 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 Argon atmosphere. Elemental analyses were effected by the microanalitical laboratory of Dipartimento di Chimica, University of Ferrara.

Mixture of *syn* and *anti (3R,4S)*-3,4-*O*-Isopropylidencyclohexan-1-one-*O*-*p*-toluenesulfonyl-oximes 8.

To a solution of **7** (2.5g, 14.5mmol) in ethanol 95% (200ml), hydroxylamine hydrochloride (5.7g, 83.5mmol) and CH_3COONa (3.9g, 48mmol) were added and the mixture stirred at room temperature for 1.5h, then evaporated, diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The dried organic phase was evaporated to afford the unseparable mixture of oxime derivatives (2.2g, 79%) which was dissolved in pyridine (10 ml), cooled at -20°C and treated with *p*-toluenesulfonylchloride (3.3g, 17.4mmol) added in small portions.

The reaction mixture was stirred at -20°C for 1h and at -10°C for an additional hour, then ice-water was added and the corresponding sulfonates **8** quantitatively recovered by ether extraction (4.9g) as a yellow solid, m.p. 100°C with decomposition.

***(5S,6R)*-5,6-*O*-Isopropylidene-hexahydroazepin-2-one 9 and *(4S,5R)*-4,5-*O*-Isopropylidene-hexahydroazepin-2-one 10.**

A solution of the mixture of the oxime sulfonates **8** (4.9g, 14.45mmol) in benzene (50ml) was adsorbed on a column of basic alumina (100g) and eluted with light petroleum, CH_2Cl_2 and methanol. The methanolic fractions were evaporated and the residue purified by flash-chromatography (eluent: EtOAc : MeOH 9.5: 0.5) to afford the mixture of the isomeric lactames **9** and **10** (1.3 g, 50%), from which pure **9** (0.67g) was obtained by fractional crystallization (EtOAc : *n*-pentane) as a white solid, m.p. 84-86°C, $[\alpha]_D^{25}$ =+46.1° (c 0.98, $CHCl_3$). IR (KBr): 1680 cm^{-1}. ^1H NMR: δ 1.36 (s; 3H); 1.48 (s; 3H); 1.9-2.3 (m; 3H); 2.83-3.15 (m; 2H); 3.3-3.5 (m; 1H); 4.0-4.1 (m; 1H); 4.3-4.4 (m; 1H); 7.15 (br. s; 1H). ^{13}C NMR: δ 23.96; 25.73; 28.18; 29.49; 41.80; 74.47; 74.84; 107.83; 177.95. Anal. Calcd. for $C_9H_{15}NO_3$ requires C, 58.35; H, 8.17; N, 7.56. Found: C, 58.27; H, 8.10; N, 7.64.

***(3R,4S)*-*N*-*p*-Toluensulfonyl-3,4-*O*-isopropylidene-hexahydroazepine 11 and *meso*-*N*-*p*-Toluensulfonyl-4,5-*O*-isopropylidene-hexahydroazepine 12.**

A solution of **9** and **10** (0.7g, 3.78mmol) in THF (30ml) was added dropwise to a cooled (0°C) slurry of $LiAlH_4$ (0.92g, 24mmol) in THF (100ml) and the reaction mixture stirred at room temperature for 2h. Saturated aqueous NH_4Cl solution was added and the mixture extracted with EtOAc. The combined organic phases were dried and concentrated. The residue was dissolved in pyridine (6ml), cooled at -20°C, treated portionwise with *p*-toluenesulfonylchloride (0.8g, 4.2mmol) and the mixture stirred at the same temperature for 1h. Ice-water was added and the mixture extracted with ether. The combined organic extracts were dried, the solvent removed under reduced pressure and the residue purified by flash-chromatography (EtOAc : light petroleum 2:8) to give **11** (0.71g) and **12** (0.12g) in 68% overall yield. By applying the same protocol to the crystalline lactam **9** the isomer **11** could be isolated as the sole product in 72% yield, m.p. 91-92°C (EtOAc : light petroleum), $[\alpha]_D^{25}$ =-32.7° (c 1.27, $CHCl_3$); IR (Kbr): 2920, 1335, 1150 cm^{-1}; ^1H NMR: δ 1.33 (s; 3H); 1.41 (s; 3H); 1.6-2.1 (m; 4H); 2.42 (s; 3H); 2.6-2.9 (m; 2H); 3.7 (m; 2H); 4.4 (m; 2H); 7.3 (d; J=8.2; 2H); 7.65 (d; J=8.2; 2H). ^{13}C NMR: δ 21.62; 24.25; 24.79; 27.56; 28.95; 48.96; 51.30; 77.08; 77.95; 109.25; 127.85; 130.60; 136.51; 144.33.

12: m.p. 152°C (EtOAc : light petroleum). IR (KBr):2920; 1335; 1170; cm^{-1}; ^1H NMR: δ 1.31 (s; 3H); 1.37 (s; 3H); 1.6-2.3 (m; 4H); 2.42 (s; 3H); 3-3.2 (m; 2H); 3.3-3.6 (m; 2H);4.38 (m; 2H); 7.3 (d; J=8.4; 2H); 7.65 (d; J=8.4; 2H). ^{13}C NMR: δ 21.67; 23.89; 26.38; 32.20; 43.89; 76.43; 107.61; 127.94; 130.55; 136.64; 144.18.

Anal. Calcd. for $C_{16}H_{23}NO_4S$ requires C, 59.05; H, 7.13; N, 4.31. Found: C, 58.92; H, 7.20; N, 4.41.

***(3R,4S)*-*N*-*p*-Toluensulfonyl-3,4-dihydroxy-hexahydroazepine 13.**

A solution of **11** (0.5g, 1.54mmol) in methanol (15ml) was stirred at room temperature for 1h in the presence of 5% HCl (10ml). Evaporation of the solvents gave **13** (0.45g, 90%) as a white solid, m.p. 92-94°C (EtOAc : light petroleum). $[\alpha]_D^{25}$=-24.3° (c 0.79, MeOH). IR (KBr): 3300; 1360; 1170 cm^{-1}; ^1H NMR: δ 1.5-1.8 (m; 3H); 1.9-2.1 (m; 1H); 2.43 (s; 3H); 2.53 (d; J=5.5; 1H); 2.80 (d; J=5.9; 1H); 3.2-3.4 (m; 4H); 3.8 (m; 1H); 3.93 (m;

1H); 7.3 (d; J=8.2; 2H); 7.68 (d; J=8.3; 2H). Anal. Calcd. for $C_{13}H_{19}NO_4S$ requires C, 54.72; H, 6.72; N, 4.91. Found: C, 54.78; H, 6.74; N, 4.95.

***(3R,4S)*-3,4-*O*-Benzylidene-*N*-*p*-toluenesulfonyl-hexahydroazepine 14.**

To a mixture of **13** (1.1g, 3.8mmol) and benzaldehyde dimethylacetal (5ml) catalytic *p*-toluenesulfonic acid was added. After being stirred at room temperature for 30min the resulting solution was flash chromatographed on silica gel (ether: light petroleum 4:6) affording white solid **14** (1.2g, 85%) as an inseparable mixture of diastereomers, epimers at the acetal carbon. IR (KBr):1360; 1170 cm^{-1}; ^1H NMR: δ 1.6-2.2 (m; 4H); 2.42 (s; 3H); 2.6-3.0 (m; 2H); 3.7-4.0 (m; 2H); 4.4-4.6 (m; 2H); 5.79 and 6.11 (s; 1H); 7.3-7.8 (m; 9H). Anal. Calcd. for $C_{20}H_{23}NO_4S$ requires C, 64.32; H, 6.21; N, 3.75. Found: C, 64.39; H, 6.18; N, 3.72.

***(3R,4R)*-*N*-*p*-Toluenesulfonyl-3-benzoyloxy-4-bromo-hexahydroazepine 15 and *(3S,4S)*-*N*-*p*-Toluenesulfonyl-4-benzoyloxy-3-bromo-hexahydroazepine 16.**

To a solution of **14** (2.45g, 6.6mmol) in CCl_4 (40ml), N-bromosuccinimide (1.3g, 7.2mmol) and a catalytic amount of α,α'-azoisobutyronitrile were added. The reaction mixture was heated at reflux for 30min then cooled at room temperature and washed with brine. The organic phase was dried, the solvent was removed, and the residue purified by flash-chromatography (ether: light petroleum 4: 6) yielding the mixture of the regioisomers **15** and **16** (3.4g, 95%), from which pure **15** was obtained by crystallization (EtOAc: hexane), m.p. 112-113°C, $[\alpha]_D^{25}$ =+9.6° (c 0.87, $CHCl_3$). IR (KBr): 1720; 1350; 1170 cm^{-1}. ^1H NMR: δ 1.8-2.2 (m; 3H); 2.4 (s; 3H); 2.4-2.6 (m; 1H); 3.0 (m; 1H); 3.44 (dd; J=15.4; J=4.7; 1H); 3.6 (m; 1H); 3.9 (dd; J=4.7; J=15.4; 1H); 4.43 (m; 1H); 5.33 (m; 1H); 7.26-8.15 (m; 9H); ^{13}C NMR: δ 21.49; 25.09; 30.56; 47.80; 48.06; 52.88; 75.72; 127.10; 128.43; 129.77; 130.03; 133.25; 135.8; 143.45; 165.7. Anal. Calcd. for $C_{20}H_{22}BrNO_4$ requires C, 57.27; H, 5.29; N, 3.34. Found: C, 57.35; H, 5.25; N, 3.33.

***(3R,4S)*-*N*-*p*-Toluenesulfonyl-3,4-epoxy-hexahydroazepine (-)17.**

To a solution of isomeric bromobenzoyl derivatives **15** and **16** (0.55g, 1.21mmol) in methanol (20ml), MeONa (70mg, 1.21mmol) was added and the mixture stirred at room temperature for 2.5h. Most of the solvent was removed under reduced pressure and the residue partitioned between ether and saturated NH_4Cl solution. The ethereal phase was separated, dried and concentrated. The residue was purified by flash-chromatography (ether: light petroleum 6: 4) to afford **(-)17** (0.25g, 78%) as a solid, m.p. 79-80°C, $[\alpha]_D^{25}$ =-8.2° (c 1.25, CH_2Cl_2). IR (KBr): 1610; 1350; 1180 cm^{-1}; ^1H NMR in C_6D_6 is in complete accord with that reported for the enantiomer by Tanner *et al.*[4,5]. Anal. Calcd. for $C_{13}H_{17}NO_3S$ requires C, 58.41; H, 6.41; N, 5.24. Found: C, 58.35; H, 6.46; N, 5.28.

***(3R,4S)*-*N*-*p*-Toluenesulfonyl-4-azido-3-benzoyloxy-hexahydroazepine 22.**

To a solution of **15** (3.5g, 8.3mmol) in DMF (50ml), NaN_3 (3g, 46.2mmol) was added and the mixture heated at 80 °C for 24h. The solvent was evaporated, the residue was diluted with EtOAc and the solution was washed with brine. After anhydrification and solvent evaporation, the crude residue was purified by flash-chromatography (ether: light petroleum 4: 6) affording **22** (2.4g, 70%) as a solid, m.p. 84-85°C (EtOAc: pentane), $[\alpha]_D^{25}$ =-86.5° (c 0.99, $CHCl_3$). IR (KBr): 2100; 1740; 1610; 1350; 1180 cm^{-1}; ^1H NMR: δ 1.8-2.3 (m;4H); 2.39 (s; 3H); 3.0-3.2 (m; 1H); 3.32 (dd; J= 8.0; 14.5; 1H); 3.5-3.7 (m; 1H); 3.78 (dd; J=4.3; 14.5;

1H); 4.0 (m; 1H); 5.35 (m; 1H); 7.3-8.1 (m; 9H); ^{13}C NMR: δ 21.58; 23.18; 26.20; 47.51; 47.93; 62.07; 74.40; 127.03; 128.55; 129.44; 129.87; 129.96; 133.50; 136.06; 143.56; 165.32. Anal. Calcd. for $C_{20}H_{22}N_4O_4S$ requires C, 57.95; H, 5.35; N, 13.53. Found: C, 57.90; H, 5.33; N, 13.56.

***(3R,4S)-N-p*-Toluenesulfonyl-4-azido-3-*O*-methylsulfonyl-hexahydroazepine 23.**

To a solution of **22** (2.15g, 5.2mmol) in MeOH (40ml), solid K_2CO_3 (0.5g) was added and the mixture was stirred at room temperature for 1h. Most of the solvent was evaporated in vacuum, the residue was diluted with EtOAc and washed with brine. The dried organic phase was evaporated to give a residue that was dissolved in CH_2Cl_2 (50ml). To the cooled (0°C) solution, CH_3SO_2Cl (0.54ml, 6.7mmol) and Et_3N (0.94ml, 6.7mmol) were added. The reaction mixture was stirred at room temperature for 1h, then brine was added, the organic phase separated, dried and evaporated. The residue was purified by flash-chromatography (ether: light petroleum 7:3) to yield **23** (1.45g, 72%), m.p.122-124°C ($CHCl_3$: ether), $[\alpha]_D^{25}$ =-34.1° (c 1.46, $CHCl_3$); IR (KBr): 1610; 1350; 1180 cm^{-1} ; ^1H NMR: δ 1.7-2.2 (m; 4H); 2.43 (s; 3H); 2.9 (m; 1H); 3.16 (s; 3H); 3.2 (dd; J=8.0; 14.5; 1H); 3.7 (m; 1H); 3.8 (dd; J=5.4; 14.5; 1H); 4.15 (m; 1H); 4.9 (m; 1H); 7.32 (d; J=8.2; 2H); 7.66 (d; J=8.2; 2H). Anal. Calcd. for $C_{14}H_{20}N_4O_5S_2$ requires C, 43.29; H, 5.19; N, 14.43. Found: C, 43.24; H, 5.21; N, 14.45.

***(3S,4S)-N-p*-Toluenesulfonyl-3-acetyloxy-4-azido-hexahydroazepine 24.**

To a stirred solution of **23** (0.65g, 1.67mmol) in anhydrous benzene (30ml) CsOAc (0.96g, 5mmol) and 18-Crown-6 (0.22g, 0.83mmol) were added and the mixture was heated at reflux for 36h. The cooled mixture was diluted with EtOAc and washed with brine. The organic phase was separated, dried and concentrated under reduced pressure. Purification of the residue by flash-chromatography (ether : light petroleum 7: 3) yielded **24** (0.56g, 95%) as an oil. $[\alpha]_D^{25}$ =-13.7° (c 0.73, $CHCl_3$). IR (neat): 2200; 1760; 1360; 1180 cm^{-1}. ^1H NMR: δ 1.6-2.1 (m; 4H); 2.16 (s; 3H); 2.41 (s; 3H); 2.80 (m; 1H); 3.1 (dd; J=3.1; 15.5; 1H); 3.5-3.8 (m; 3H); 4.7 (m; 1H); 7.3 (d; J=8.1; 2H); 7.65 (d; J=8.1; 2H); ^{13}C NMR: δ 21.19; 21.55; 24.67; 27.67; 48.23; 49.14; 64.02; 74.81; 127.14; 129.85; 135.73; 143.61; 170.41. Anal. Calcd. for $C_{15}H_{20}N_4O_4S$ requires C, 51.12; H, 5.72; N, 15.91. Found: C, 51.16; H, 5.69; N, 15.94.

***(3S,4S)-N-p*-Toluenesulfonyl-4-azido-3-hydroxy-hexahydroazepine 21.**

To a solution of **24** (0.26g, 0.74mmol) in MeOH (10ml), solid K_2CO_3 (0.1g) was added and the mixture was stirred at room temperature for 15min then after partial solvent evaporation the residue was partitioned between brine and EtOAc, the organic phase separated, dried and concentrated. Flash-chromatography of the residue (ether: light petroleum 6:4) afforded **21** (0.2g, 87%), $[\alpha]_D^{25}$ =+5° (c 0.48, CH_2Cl_2) as a white solid, m.p. 119-120°C (EtOAc : pentane). Anal. Calcd. for $C_{13}H_{18}N_4O_3S$ requires C, 50.30; H, 5.85; N, 18.06. Found: C, 50.33; H, 5.84; N, 18.09.

***(3R,4S)-N-p*-Toluenesulfonyl-3,4-*O*-sulfonyl-hexahydroazepine 18.**

To a cooled (0 °C) solution of **13** (0.6g, 2.1mmol) in CH_2Cl_2 (30ml) containing triethylamine (1.2ml, 8.5mmol), thionyl chloride (0.55ml, 7.5mmol) was added dropwise. The reaction mixture was stirred at room temperature for 15min then was diluted with ether and washed with cold (0°C) water. The dried organic phase was concentrated and the residue poured into a mixture of CCl_4 (20ml), CH_3CN (20ml) and water (30ml). The resulting solution was cooled at 0°C and a catalytic amount of $RuCl_3$ and $NaIO_4$ (0.91g, 4.26mmol) was added. After 1h stirring, the mixture was diluted with ether and the phases were separated. The aqueous phase was

extracted twice with ether and the combined organic extracts were dried and evaporated under reduced pressure. The residue, purified by flash-chromatography (EtOAc : light petroleum 3: 7), yielded **18** (0.7g, 96%) as a white solid, m.p. 115-117°C, $[\alpha]_D^{25}$=-24.35° (c 0.78, $CHCl_3$). IR (KBr): 1360; 1180 cm^{-1}; ^1H NMR: δ 1.7-2.4 (m; 4H); 2.45 (s; 3H); 2.76 (m; 1H); 3.14 (dd; J=10.2; 14.8; 1H); 3.81 (m; 1H); 3.97 (dd; J=5.1; 15; 1H); 5.1-5.3 (m; 2H); 7.35 (d; J=8.2; 2H); 7.68 (d; J=8.2; 2H). Anal. Calcd. for $C_{13}H_{17}NO_6S_2$ requires C, 44.95; H, 4.94; N, 4.03. Found: C, 44.98; H, 4.96; N, 4.05.

***(3R,4R)*-*N*-*p*-Toluenesulfonyl-4-benzoyloxy-3-hydroxy-hexahydroazepine 19.**

A solution of **18** (0.42g, 1.22mmol) and ammonium benzoate (0.34g, 2.44mmol) in DMF (20ml) was heated at 80°C for 24h.The solvent was evaporated and the residue dissolved in THF. To the solution one drop of concentrated H_2SO_4 and water (22μl, 1.22mmol) were added and the mixture was heated at reflux for 2h. The solvent was evaporated and the residue diluted with EtOAc (20ml) and washed with saturated $NaHCO_3$ solution. The dried organic phase was evaporated to give a crude oil from which compound **19** (0.35g, 74%) was obtained after flash-chromatography (EtOAc : light petroleum 4: 6). IR (neat): 3300; 1740; 1360; 1180 cm^{-1}; ^1H NMR: δ 1.8-2.2 (m; 4H); 2.43 (s; 3H); 3.24 (m; 1H); 3.4-3.6 (m; 3H); 4.0 (m; 1H); 5.1 (m; 1H); 7.3-8.2 (m; 9H). Anal. Calcd. for $C_{20}H_{23}NO_5S$ requires C, 61.68; H, 5.96; N, 3.60. Found: C, 61.72; H, 5.95; N, 3.65.

***(3R,4R)*-*N*-*p*-Toluenesulfonyl-4-benzoyloxy-3-*O*-methylsulfonyl-hexahydroazepine 20.**

To a cooled (0°C) solution of **19** (0.3g, 0.77mmol) in CH_2Cl_2 (20ml) Et_3N (140μl, 1mmol) and CH_3SO_2Cl (78μl, 1mmol) were added and stirring was continued at room temperature for 1h. The reaction mixture was washed with brine and the separated organic phase was dried and evaporated to give a residual oil that was purified by flash-chromatography (EtOAc : light petroleum 4: 6) yielding **20** (0.35g, 97%) as a white solid, m.p. 140-141°C (EtOAc : light petroleum), $[\alpha]_D^{25}$ =-88° (c 0.375, $CHCl_3$). IR (KBr): 1740; 1360; 1180 cm^{-1}. ^1H NMR: δ 1.8-2.2 (m; 4H); 2.44 (s; 3H); 3.06 (s; 3H); 3.3 (m; 2H); 3.49 (dd; J=16.3; 7.2; 1H); 3.7 (dd; J=16.3; 3.9; 1H); 4.98 (m; 1H); 5.19 (m; 1H); 7.3-8.2 (m; 9H); ^{13}C NMR: δ 21.63; 22.99; 27.04; 38.49; 48.12; 48.34; 75.77; 80.03; 127.20; 128.64; 129.54; 129.82; 130.01; 133.53; 135.50; 143.90; 165.50. Anal. Calcd. for $C_{21}H_{25}NO_7S_2$ requires C, 53.95; H, 5.39; N, 3.00. Found: C, 53.99; H, 5.41; N, 2.99.

***(3S,4R)*-*N*-*p*-Toluenesulfonyl-3,4-epoxy-hexahydroazepine (+)17.**

A solution of **20** (0.1g, 0.21mmol) in methanol (10ml) was treated with MeONa (12mg, 0.22mmol) and stirred at room temperature for 2.5h. The solvent was evaporated, the residue diluted with ether and washed with saturated NH_4Cl solution. Evaporation of the dried organic phase was followed by flash-column chromatography (ether : light petroleum 6: 4) to afford **(+)17** (53mg, 95%) as a crystalline solid, m.p. 79-80°C, $[\alpha]_D^{25}$ =+6.8° (c 1.0, CH_2Cl_2).

***(1S,3R,4S)*-1-*O*-Methylsulfonyl-3,4-*O*-isopropylidene-cyclohexane 27 and *(1R,3R,4S)*-1-*O*-Methylsulfonyl-3,4-*O*-isopropylidene-cyclohexane 28.**

To a cooled (0°C) solution of **7** (2.6g, 15.3mmol) in MeOH (30ml) $NaBH_4$ (0.87g, 23mmol) was added and the mixture stirred for 30min at room temperature. After solvent removal the residue was diluted with EtOAc and washed with brine. The dried organic phase was evaporated to give a residue which was dissolved in CH_2Cl_2 (30ml). To the cooled (0°C) solution, Et_3N (2.7ml, 19mmol) and CH_3SO_2Cl (1.5ml, 19mmol) were added and

stirring was continued at room temperature for 1h. The mixture was washed with brine and the organic extract was dried and evaporated. The residue, flash-chromatographed on silica gel (ether: light petroleum 7: 3) yielded **27** (0.26g, 6.9%) and **28** (2.9g, 76.7%).

27: $[\alpha]_D^{25}$ =+22° (c 1.3, $CHCl_3$). ^1H NMR: δ 1.33 (s; 3H); 1.48 (s; 3H); 1.7-2.3 (m; 6H); 3.01 (s; 3H); 4.2 (m; 1H); 4.32 (m; 1H); 5.0 (m; 1H).

28: $[\alpha]_D^{25}$ =+47.8° (c 1.3, $CHCl_3$). IR (neat): 2980 cm^{-1}. ^1H NMR: δ 1.47 (s; 3H); 1.65 (s; 3H); 1.8-2.2 (m; 4H); 2.3-2.5 (m; 2H); 3.16 (s; 3H); 4.2-4.4 (m; 2H); 4.7-4.9 (m; 1H). Anal. Calcd. for $C_{10}H_{18}O_5S$ requires C, 47.98; H, 7.25. Found: C, 47.95; H, 7.23.

***(1S,3R,4S)*-1-Azido-3,4-*O*-isopropylidene-cyclohexane 29.**

To a solution of **28** (2.8g, 11.2mmol) in DMF (40ml), NaN_3 (3.8g, 59mmol) was added and the mixture heated at 80°C for 24h. The solvent was evaporated, the residue diluted with EtOAc and the solution washed with brine. The organic extract was dried and evaporated. The crude residue was purified by flash-chromatography (ether : light petroleum 1: 9) affording **29** (1.7g, 77%), $[\alpha]_D^{25}$ =+8.2° (c 1.0, $CHCl_3$). IR (neat): 2980; 2140 cm^{-1}. ^1H NMR: δ 1.35 (s; 3H); 1.49 (s; 3H); 1.6-1.9 (m; 5H); 2.1-2.3 (m; 1H); 3.7-3.9 (m; 1H); 4.1-4.25 (m; 1H); 4.25-4.4 (m; 1H). Anal. Calcd. for $C_9H_{15}N_3O_2$ requires C, 54.79; H, 7.67; N, 21.31. Found: C, 54.74; H, 7.65; N, 21.38.

***(1S,3R,4S)*-1-Azido-3,4-dihydroxy-cyclohexane 30.**

A solution of **29** (0.75g, 3.8mmol) in MeOH (10ml) was stirred for 15min at room temperature in the presence of 5% HCl (10ml). Removal of solvents gave **30** (0.58g, 98%) as a white solid, m.p. 51-52°C (ether : *n*-pentane), $[\alpha]_D^{25}$ =+17.5° (c 1.1, $CHCl_3$); IR (KBr): 3400; 2960; 2140 cm^{-1}; ^1H NMR: δ 1.3-2.3 (m; 8H); 3.7-3.9 (m; 2H); 3.9-4.1 (m; 1H). Anal. Calcd. for $C_6H_{11}N_3O_2$ requires C, 45.84; H, 7.06; N, 26.74. Found: C, 45.87; H, 7.03; N, 26.80.

***(1S,3R,4S)*-1-Azido-3,4-dibenzoyloxy-cyclohexane 31, *(1S,3R,4S)*-1-Azido-4-benzoyloxy-3-hydroxy-cyclohexane 32 and *(1S,3R,4S)*-1-Azido-3-benzoyloxy-4-hydroxy-cyclohexane 33.**

To a cooled (0°C) solution of **30** (1.1g, 7mmol) in CH_2Cl_2 (30ml), a catalytic amount of DMAP, benzoyl chloride (1.1ml, 10mmol) and Et_3N (1.4ml, 10mmol) were added. After being stirred for 12h at room temperature the solution was washed with brine and the dried organic phase was evaporated. Flash-chromatography (ether: light petroleum 1: 1) of the residue afforded **31** (0.14g), **32** (0.9g) and **33** (0.57g).

31: $[\alpha]_D^{25}$ =+19.8° (c 0.65, $CHCl_3$). IR (neat): 3100; 2980. 2140; 1730 cm^{-1}; ^1H NMR: δ 1.6-2.5 (m; 6H); 3.97 (m; 1H); 5.36 (m; 1H); 5.63 (m; 1H); 7.3-7.7 (m; 6H); 7.9-8.1 (m; 4H). Anal. Calcd. for $C_{20}H_{19}N_3O_4$ requires C, 65.74; H, 5.24; N, 11.50. Found: C, 65.79; H, 5.20; N, 11.55.

32: $[\alpha]_D^{25}$ =+17° (c 1.1, $CHCl_3$). IR (neat): 3500; 3100; 2980. 2140; 1730; 1620; 1470 cm^{-1}; ^1H NMR: δ 1.5-2.3 (m; 7H); 3.9-4.1 (m; 1H); 4.2-4.35 (m; 1H); 5.1-5.3 (m; 1H); 7.4-7.7 (m; 3H); 8.0-8.15 (m; 2H).

33: $[\alpha]_D^{25}$ =+36.8° (c 0.9, $CHCl_3$). IR (neat): 3500; 3100; 2980. 2140; 1730; 1620; 1470 cm^{-1}; ^1H NMR: δ 1.4-2.4 (m; 7H); 3.8-4.0 (m; 1H); 4.0-4.1 (m; 1H); 5.3-5.4 (m; 1H); 7.3-7.6 (m; 3H); 8.0-8.1 (m; 2H). Anal. Calcd. for $C_{13}H_{15}N_3O_3$ requires C, 59.74; H, 5.79; N, 16.09. Found: C, 59.79; H, 5.76; N, 16.12.

***(1S,3R,4S)*-1-Azido-3-benzoyloxy-4-*O*-methylsulfonyl-cyclohexane 34.**

To a cooled (0°C) solution of **33** (0.79g, 3mmol) in CH_2Cl_2 (20ml), Et_3N (0.55ml, 3.9mmol) and CH_3SO_2Cl (0.3ml, 3.9mmol) were added and stirring was continued for 1h at room temperature. The reaction mixture was washed with brine and the organic phase, dried and evaporated, gave a residue that was purified by flash-chromatography (ether: light petroleum 7: 3) to afford **34** (0.95g, 95%) as a white solid, m.p. 118-120°C, $[\alpha]_D^{25}$=+39.5° (c 0.75, $CHCl_3$). IR (neat): 2980; 2140; 1740; 1640; 1470 cm^{-1}; ^1H NMR: δ 1.7-2.4 (m; 6H); 2.99 (s; 3H); 3.9-4.1 (m; 1H); 5.0-5.15 (m; 1H); 5.4-5.5 (m; 1H); 7.4-7.6 (m; 3H); 8.0-8.2 (m; 2H). Anal. Calcd. for $C_{14}H_{17}N_3O_5S$ requires C, 49.54; H, 5.05; N, 12.39. Found: C, 49.58; H, 5.07; N, 12.42.

***(1S,3R,4S)*-1-Amino-3-benzoyloxy-4-*O*-methylsulfonyl-cyclohexane 35.**

A solution of **34** (1g, 2.95mmol) in EtOAc (20ml) was hydrogenated in the presence of 10% C/Pd (0.1g) for 3h at 50psi in a Parr apparatus. Removal of the catalyst by filtration and solvent evaporation gave a residue that was flash-chromatographed (CH_2Cl_2: $CHCl_3$: MeOH: NH_4OH; 100: 40: 9: 1) giving **35** (0.81g, 88%) as an oil, $[\alpha]_D^{25}$ =-6.4° (c 0.86, $CHCl_3$); IR (neat): 3400; 2970; 1760; 1640; 1460 cm^{-1}; ^1H NMR: δ 1.3-1.7 (m; 4H); 2.0-2.4 (m; 4H); 3.0 (s; 3H); 3.2-3.4 (m; 1H); 4.8-5.0 (m; 1H); 5.1-5.25 (m; 1H); 7.4-7.7 (m; 3H);8.0-8.1 (m; 2H). Anal. Calcd. for $C_{14}H_{19}NO_5S$ requires C, 53.66; H, 6.12; N, 4.47. Found: C, 53.69; H, 6.10; N, 4.50.

***(1R,2R,4S)*-2-Benzoyloxy-7-azabicyclo[2.2.1]heptane 36.**

A solution of **35** (0.92g, 2.94mmol) in toluene (40ml) was heated at reflux for 4 days, then washed with saturated $NaHCO_3$ solution. The dried organic extract was evaporated to give **36** (0.6g, 95%) as an oil, $[\alpha]_D^{25}$ =+17.1° (c 0.49, $CHCl_3$); IR (neat): 3400-3300; 3000; 1730; 1600; 1460 cm^{-1}; ^1H NMR: δ 1.28 (dd; J=13.2; 3.4; 1H); 1.5-1.75 (m; 3H); 1.86 (s; 1H); 2.0-2.3 (m; 2H); 3.66 (t; J=4.6; 1H); 3.91 (t; J=4.6; 1H); 5.0-5.2 (m; 1H); 7.4-7.7 (m; 3H); 8.0-8.1 (m; 2H). Anal. Calcd. for $C_{13}H_{15}NO_2$ requires C, 71.85; H, 6.96; N, 6.45. Found: C, 71 91; H,6.93 ; N, 6.48.

***(1R,2R,4S)*-*N*-Benzyl-2-hydroxy-7-azabicyclo[2.2.1]heptane 37.**

To a solution of **36** (100mg, 0.46mmol) in DMF (30ml), K_2CO_3 (70mg) and benzyl bromide (60μl, 0.5mmol) were added and the mixture heated at 60°C for 3h. Most of the solvent was evaporated, water (20ml) was added and the mixture extracted with EtOAc. The residue deriving from evaporation of the dried organic phase was dissolved in MeOH (20ml) and K_2CO_3 (70mg) was added to the solution. After stirring at room temperature for 2h and solvent removal, the residue was purified by flash-chromatography (CH_2Cl_2: $CHCl_3$: MeOH: NH_4OH; 100: 40: 9: 1) to afford **37** (66mg, 71%), $[\alpha]_D^{25}$ =-24.6° (c 0.65, $CHCl_3$); IR (neat): 3400; 3000; 1620; 1470 cm^{-1}; ^1H NMR: δ 0.9-1.0 (m; 1H); 1.4-2.3 (m; 5H); 2.5 (br.s; 1H); 3.1-3.3 (m; 2H); 3.5-3.65 (m; 2H); 4.2-4.4 (m; 1H); 7.25-7.5 (m; 5H); ^{13}C NMR: δ 18.35; 27.25; 39.74; 51.98; 60.59; 63.95; 71.01; 126.92; 128.29; 128.67; 139.46. Anal. Calcd. for $C_{13}H_{17}NO$ requires C, 76.80; H, 8.43; N, 6.89. Found: C, 76.74; H, 8.45; N, 6.91.

***(1S,3R,4S)*-1-Azido-4-benzoyloxy-3-*O*-methylsulfonyl-cyclohexane 38.**

This compound was obtained from **32** using the same procedure as above described for **34**, $[\alpha]_D^{25}$ =+14.9° (c 0.825, $CHCl_3$); IR (neat): 3400; 2970; 1760; 1640; 1460 cm^{-1}; ^1H NMR: δ 1.3-1.5 (m; 2H); 1.6-1.8 (m; 1H); 1.9-2.2 (m; 2H); 2.3-2.45 (m; 1H); 2.97 (s; 3H); 3.2-3.4 (m; 1H); 5.1-5.3 (m; 2H); 7.4-7.7 (m; 3H); 8.0-8.2

(m; 2H). Anal. Calcd. for $C_{14}H_{17}N_3O_5S$ requires C, 49.54; H, 5.05; N, 12.39. Found: C, 49.58; H, 5.07; N, 12.41.

***(1S,3R,4S)*-1-Amino-4-benzoyloxy-3-*O*-methylsulfonyl-cyclohexane 39.**

This compound was obtained from **38** using the same procedure already described for **35**. $[\alpha]_D^{25}$ =-10.6° (c 0.575, $CHCl_3$); IR (neat): 3400; 2970; 1760; 1640; 1460 cm^{-1}; ^1H NMR: δ 1.4 (m; 3H); 1.6-1.8 (m; 1H); 2.0 (m; 3H); 2.3-2.5 (m; 1H); 2.9 (s; 3H); 3.2-3.4 (m; 1H); 5.0-5.3 (m; 2H); 7.4-7.7 (m; 3H); 8.0-8.1 (m; 2H). Anal. Calcd. for $C_{14}H_{19}NO_5S$ requires C, 53.66; H, 6.12; N, 4.47. Found: C, 53.70; H, 6.15; N, 4.45.

***(1S,3R,4S)*-1-Azido-3,4-*O*-sulfonyl-cyclohexane 40.**

To a cooled (0°C) solution of **30** (0.1g, 0.63mmol) in CH_2Cl_2 (6ml), Et_3N (0.3ml, 2.5mmol) and $SOCl_2$ (0.16ml, 2.5mmol) were successively added. The reaction mixture was kept at room temperature for 15min, then diluted with ether (20ml) and washed with ice-water. The separated organic extract was dried and evaporated. The residue was dissolved in CCl_4 (6ml) and CH_3CN (6ml), and water (9ml) was added. The solution was cooled at 0°C and a catalytic amount of $RuCl_3$ and $NaIO_4$ (0.27g, 1.28mmol) were added. After stirring for 1h at room temperature, the reaction mixture was diluted with ether and the phases were separated. The aqueous phase was extracted twice with ether and the combined organics were dried and evaporated. Purification of the residue by flash-chromatography (ether : light petroleum 1: 1) yielded **40** (0.13g, 94%) as an oil. $[\alpha]_D^{25}$ =+49.8° (c 1.25, $CHCl_3$); ^1H NMR: δ 1.6-1.8 (m; 1H); 1.9-2.1 (m; 1H); 2.15-2.5 (m; 4H); 4.0-4.15 (m; 1H); 5.0-5.2 (m; 2H). ^{13}C NMR: δ 22.91; 24.10; 31.25; 55.07; 80.65; 80.89. Anal. Calcd. for $C_6H_9N_3O_4S$ requires C, 32.87; H, 4.14; N, 19.18. Found: C, 32.90; H, 4.12; N, 19.22.

***(1R,2R,4S)*-7-Azabicyclo[2.2.1]hept-2-yl-hydrogensulfate 41.**

To a solution of **40** (130mg, 0.59mmol) in 1:1 THF/H_2O (10ml), 10% C/Pd (30mg) was added and the mixture was hydrogenated in a Parr apparatus at 30 psi for 2h. The catalyst was removed by filtration through Celite and the solvent evaporated to give the salt **41** (90mg, 82%) that was crystallized from H_2O: dioxane, m.p.>300°C. $[\alpha]_D^{25}$=+25.9° (c 1.07, H_2O). IR (KBr): 3000; 1650 cm^{-1}; ^1H NMR (D_2O): δ 1.71 (dd; J=14.8; 3.4; 1H); 1.8-2.1 (m; 3H); 2.3-2.6 (m; 2H); 4.2 (t; J=4.8; 1H); 4.4 (t; J=4.5; 1H); 4.9 (m; 1H). ^{13}C NMR: δ 21.80; 29.07; 36.92; 61.97; 62.99; 76.39.

***(1R,2R,4S)*-*N*-*tert*-Butoxycarbonyl-2-hydroxy-7-azabicyclo[2.2.1]heptane 42.**

To the solution of **41** (0.35g, 1.81mmol) in THF (20ml), one drop of conc. H_2SO_4 and water (33 µl, 1.82mmol) were added and the mixture was heated at reflux for 1h. The solvent was evaporated and the residue was partitioned between saturated K_2CO_3 aqueous solution (3ml) and CH_2Cl_2 (10ml) A solution of $(Boc)_2O$ (0.48g, 2.18mmol) in CH_2Cl_2 (5ml) was added and the reaction mixture was stirred at room temperature for 18h. The phases were separated and the organic phase was dried and evaporated. The residue was purified by flash-chromatography (EtOAc: light petroleum 3: 7) affording **42** (0.32g, 84%) as a white solid, m.p. 70-71°C, $[\alpha]_D^{25}$=-3.8° (c 0.79, $CHCl_3$). IR (neat): 3300; 3000; 1720 cm^{-1}; ^1H NMR: δ 1.06 (dd; J=12.6; 3.4; 1H); 1.44 (s; 9H); 1.4-1.9 (m; 3H); 2.1-2.3 (m; 2H); 2.6 (br.s ; 1H); 4.1-4.25 (m; 2H); 4.3-4.5 (m; 1H). Anal. Calcd. for $C_{11}H_{19}NO_3$ requires C, 61.93; H, 8.98; N, 6.57. Found: C, 61.99; H, 8.95; N, 6.55.

***(1R,4S)-N-tert*-Butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one 43.**

To a cooled (-70°C) solution of oxalyl chloride (0.26ml, 3.02mmol) in CH_2Cl_2 (25ml) a solution of DMSO (0.4ml, 5.7mmol) in CH_2Cl_2 (5ml) was added dropwise followed, after 10min, by the addition of **42** (0.42g, 1.97mmol) in CH_2Cl_2 (20ml) and 20min later by Et_3N (1.7ml, 12mmol). The reaction mixture was allowed to warm to room temperature and washed with water. The dried organic phase was evaporated and the residue purified by flash-chromatography (EtOAc : light petroleum 1: 9) furnished the ketone **43** (0.35g, 85%), m.p. 41-42°C; $[\alpha]_D^{25}$=-75° (c 1.07, $CHCl_3$); IR (neat): 3000; 1780; 1720 cm^{-1}; ^1H NMR: δ 1.45 (s; 9H); 1.4-1.7 (m; 3H); 1.9-2.1 (m; 2H); 2.48 (dd; J=17.4; 5.4; 1H); 4.25-4.35 (m; 1H); 4.55-4.7 (m; 1H). Anal. Calcd. for $C_{11}H_{17}NO_3$ requires C, 62.52; H, 8.12; N, 6.63. Found: C, 62.57; H, 8.15; N, 6.60.

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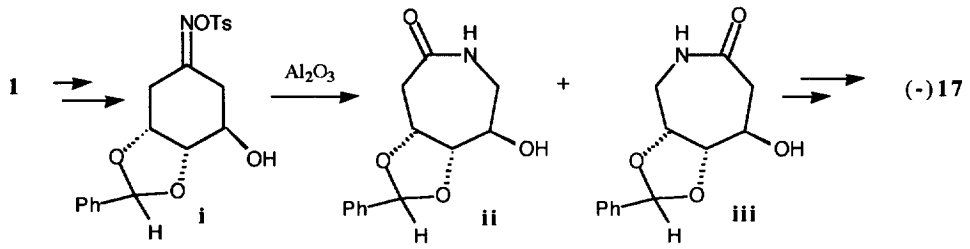

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