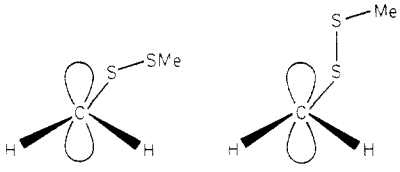
formation[14,16] for $MeSS\dot{C}H_2$, as opposed to that of the corresponding sulfide $MeS\dot{C}H_2$ that has two different H_α splittings (16.7 and 17.5 G).[8,14]

Taking advantage of our observations, we proved, however, that the same nonequivalence is present even when $MeSS\dot{C}H_2$ is produced by hydrogen abstraction with *t*-BuO·. At −50 °C the spectrum of the radical is a triplet with a 1:2:1 ratio, and its central line is symmetrically spaced with respect to the outer lines (a_{H_α} = 17.0 ± 0.1 G); on the contrary, at −110 °C there are three lines with equal intensity, and the "central" line is separated by 16.9_5 ± 0.1 G from the outer line on the left but by 17.3_5 ± 0.1 G from that on the right. This indicates that a fourth line is now missing, covered by the signals of $(t\text{-BuO})_2\dot{S}Me$.

This observation thus modifies the current ideas upon the conformation of disulfide radicals. The asymmetry we have observed requires the existence of an asymmetric conformation, and two possibilities have to be taken into account. (i) If free S–S rotation is assumed, then the SS bond cannot be, as proposed,[14,16] parallel to the direction of the p_z orbital bearing the unpaired electron (eclipsed conformation). (ii) On the other hand, if the S–S rotation is slow[17] on the ESR time scale at this temperature, then one can have nonequivalence even with an eclipsed conformation.

A choice between these two situations cannot be easily made: we wish to point out that in case i the observed barrier must be that of C–S rotation whereas in case ii the barrier is that of the faster motion between C–S and S–S rotation.



i ii

Computer simulation of the line shape yields a $\Delta G^{\ddagger}$ = 5.5 ± 0.3 kcal/mol^{-1}, a value smaller than that estimated[8] for the corresponding S–$\dot{C}H_2$ rotation in $MeS\dot{C}H_2$ (7 kcal/mol^{-1}). If we are dealing with a CS rotation, the difference might depend on the smaller steric hindrance, due to the longer SS bond with respect to the SMe bond, or to electronic effects, due to substitution of a Me with a MeS group. Obviously the difference could simply depend on the fact that the restricted motion we observed is S–S rotation (case ii) rather S–C rotation.

Experimental Section

Photolysis of MeSSMe and of MeSSMe with *t*-BuOO-*t*-Bu was carried out in cyclopropane solutions sealed in Suprasil quartz tubes within the cavity of the spectrometer. Addition of a certain amount of benzene intensifies the ESR signal of $MeSS\dot{C}H_2$ produced by direct photolysis of MeSSMe.

Since the photolysis of MeSSMe, under the very same conditions required to detect the ESR signal (low concentration and low temperature), has a very low yield, the amount of reaction products was too small for a complete analysis. However, since our aim was to obtain indications for the structure of the observed radical, rather than to study the reaction pathway, mass spectroscopy was of sufficient help for our purpose. The white solid that precipitates after photolysis at −60 °C turns out to be composed by at least two (and possibly three) products. That with the highest molecular weight (186, M^+) was identified as $CH_3S\text{-}SCH_2CH_2SSCH_3$ from its fragmentation pathway: *m/e* 139 (M − CH_3S), 107 (M − CH_3SS), and 93 (M − CH_3SSCH_2). Line-shape simulation was carried out on the computer facilities of the University of Bologna.

Acknowledgment. We thank Dr. B. P. Roberts, University College, London, for helpful comments and the Italian CNR (Rome) for financial support.

Registry No. MeSSMe, 624-92-0; $MeSS\dot{C}H_2$, 80641-42-5; $CH_3S\text{-}SCH_2CH_2SSCH_3$, 80641-43-6.

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Synthesis and Structural Verification of Novel Olefinic Derivatives of Bicyclo[2.2.2]octane. Intermediates in the Synthesis of Bridged Morphinan-Like Compounds

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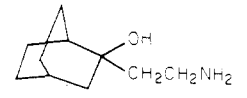
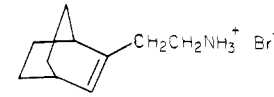
In the attempt to synthesize suitable intermediates for the preparation of novel C-ring-bridged morphinan derivatives, we have discovered, and now report, a set of reaction conditions which will provide 2-(2-aminoethyl)-bicyclo[2.2.2]oct-2-ene hydrobromide (**2**) at the expense of the exocyclic isomer **3** from the starting alcohol, 2-(2-aminoethyl)bicyclo[2.2.2]octan-2-ol (**1**).



1



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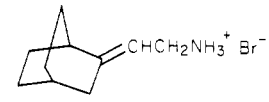

3

A priori, it appeared that for successful generation of the bicyclooctene derivative from this alcohol two criteria should be met. First, reaction conditions that favor a concerted elimination mechanism were assumed to be required in order to maintain the structural integrity of the ring system. Of the three commonly interconvertible bicyclooctane isomers, the [2.2.2] skeleton, while no more strained than the [3.2.1] or the [3.3.0] systems, is the least stable due to its low entropy.[2a] When exposed to strong ionizing conditions, derivatives of 2-substituted bicyclo-[2.2.2]octane and octene capable of forming carbonium ions will often undergo Wagner–Meerwein and related types of rearrangements[3-6] to the aforementioned isomeric forms.

(1) Supported by the American Foundation for Pharmaceutical Education as a W. Paul Briggs Memorial Fellow.
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Therefore, standard E1 elimination conditions, often employed in dehydration reactions, were avoided with this system.

Second, conditions that preferentially allow cis elimination to predominate seemed to hold the greatest promise for endocyclic elimination. The three eclipsed ethylene interactions which give bicyclo[2.2.2]octane its 8.4 kcal/mol of ring strain[2a] also allow for a true cis configuration between the leaving group and β-hydrogen in derivatives such as 1.[2b] The pseudo trans dihedral angle between the bromine and β-hydrogen of approximately 120° has been shown to greatly reduce the capacity for rapid concerted endocyclic elimination in bicyclo[2.2.2]octane and bicyclo[2.2.1]heptane derivatives.[7-9]

Equally important is the supposition that cis elimination in this system would not be expected to favor exocyclic olefin formation. Since the aminoethyl side chain of 1 is freely rotating, hydrogens of C-9 would be expected to assume the more energetically favored trans conformation in relation to the leaving group at C-2.

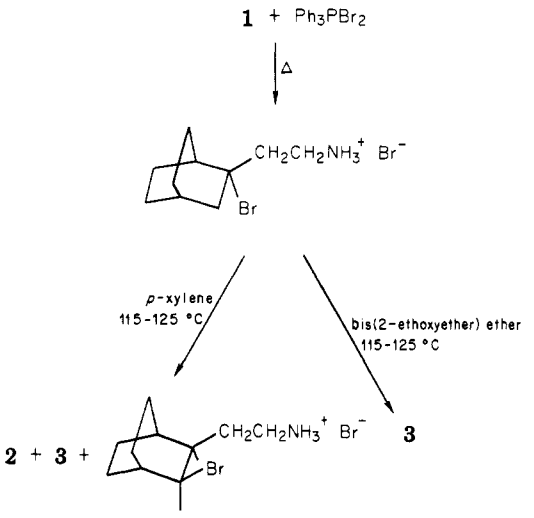
One of the more common elimination reactions involving alcohols which favor the cis configuration between the leaving group and β-hydrogen is the Chugaev reaction.[10] Unfortunately, although a number of experimental conditions appropriate for this reaction were tried,[10-12] the methyl xanthate ester of 1 did not appear to eliminate to the desired olefin, as evidenced by the lack of olefinic proton peaks in the ^1H NMR spectrum of the crude reaction mixture. The structures of these products were not further investigated.

In 1963, Kwart et al.[8] demonstrated that, under trans-favoring E2 elimination conditions, norbornyl bromide preferentially underwent cis elimination to give norbornene as 93.9% of the products isolated. Since norbornane and bicyclo[2.2.2]octane are extremely similar molecules when one considers rotational and conformational restrictions, similar elimination reaction products were expected if cis-favoring elimination conditions were employed. *exo*-Norbornyl bromide has been prepared in moderate yield by reacting *endo*-norbornanol with triphenylphosphine dibromide.[13] A modified version of this reaction was undertaken with the alcohol 1, and a thermally induced elimination was attempted.

Solvent effects are apparently important in determining the direction of elimination in this system. When bis(2-ethoxyethyl) ether was employed, the exocyclic olefinic compound 3 was the only product isolated (see Scheme I). Changing the solvent to *p*-xylene, while keeping all other reaction conditions constant, resulted in a 1:1 ratio of crude products 2 and 3.

A third product which appeared to increase in quantity with reaction time was often produced along with compounds 2 and 3 when *p*-xylene was the solvent employed. The compound, a nonolefinic base, gave a characteristic peak at 4.2 ppm in the ^1H NMR spectrum. After acylating the crude reaction mixture with (*p*-methoxyphenyl)acetyl chloride, a small amount of the substance, as the amide, was crystallized from ether/petroleum ether and gave a positive $AgNO_3$ test for halogen. This compound was

Scheme I



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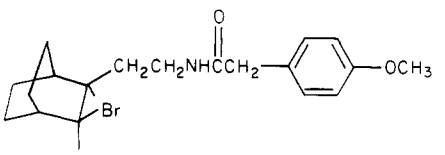
subsequently shown, spectroscopically, to be 3-bromo-[2-[[(*p*-methoxybenzyl)carbonyl]amino]ethyl]bicyclo-[2.2.2]octane (5). The data indicated that the third



5

product isolated in the dehydrohalogenation reaction had the structure represented as 4. Hydrogen bromide can add in a trans-preferring, anti-Markovnikov fashion to olefinic linkages via a free-radical process.[14] In the bicyclooctene derivative 2, such trans addition would essentially inhibit further dehydrohalogenation due to the unfavorable dihedral angle between hydrogen and bromine. This offers some explanation of why the yield of this product increased with reaction time. Further evidence to support the free-radical nature of the addition is that the formation of 4 could be inhibited by the addition of a catalytic amount of hydroquinone and protection from light.

Anti-Markovnikov addition of HBr to the exocyclic olefin 2 would be expected to reeliminate according to Zaitsev's rule, regenerating 3.

Although experiments have not been conducted to prove mechanistic pathways, perhaps the use of the more polar bis(2-ethoxyethyl) ether as the solvent allows for the stabilization of an ion pair which might prefer exocyclic trans elimination due to the greater ease with which a coplanar transition state could be reached.

Confirming the retention of the bicyclo[2.2.2]octane skeletal structure in both products 2 and 3 is the fact that only eight lines are seen in the ^{13}C NMR spectra of these ten carbon compounds. The symmetry of 2 and 3 is such that C-5 and C-8 are equivalent and appear as one line, as do C-6 and C-7. Examination of the ^{13}C NMR spectra of possible bicyclo[3.2.1]- and -[3.3.0]octanones indicated that no common rearranged bicyclooctane skeleton has this same type of symmetry.[15,16] Clearly the bicyclo[2.2.2]-

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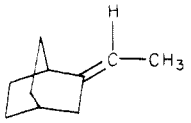
Table I. ^{13}C Chemical Shifts for 2-Substituted Bicyclo[2.2.2]octanes and Octenes

	shift, δ									
compd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
3[a]	36.09[d]	154.44[c]	32.63[e]	26.18[d]	25.79[e]	26.50[e]	26.50[e]	25.79[e]	110.89[d]	37.47[e]
6[b]	35.8	142.6	33.1	26.5	26.1	27.2	27.2	26.1	113.8	12.4
7[b]	27.7	141.3	36.5	26.6	26.1	26.3	26.3	26.1	114.4	12.6
2[a]	34.10[d]	142.25[c]	130.47[d]	30.48[d]	26.15[e]	26.55[e]	26.55[e]	26.15[e]	38.93[e]	32.98[e]
8[b]	35.3	141.9	126.6	30.1	25.6	26.8	26.8	25.6	20.3	

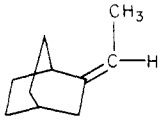
[a] Referenced to dioxane. [b] Referenced to Me_4Si. [c] Singlet. [d] Doublet. [e] Triplet.

octane skeletal structure has been maintained.

The similarity in the ^{13}C chemical shifts between **3** and the exocyclic ethylidene derivative **6** is striking[17] (see Table I). The ^{13}C chemical shifts for all ring carbons in **3** are within 0.7 ppm of those cited for **6** with the exception of the quaternary olefinic carbon, C-2, which is shifted 11.8 ppm downfield in **3**. This observation, at present, remains unexplained.



6



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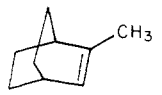

8

Carbons α to a protonated nitrogen generally show a 26-ppm downfield shift from the comparable nonnitrogen containing molecules,[18] and the chemical shift of C-10 of **3** (25.1 ppm downfield from that of **6**) fulfills empirical expectations.

Also relevant is the significantly better fit of the ^{13}C chemical shifts of **3** with those of **6** as compared to those of isomer **7**. The mean difference in chemical shift of ring carbons between compounds **3** and **6** is 1.9 ppm. A similar comparison of **3** with **7** shows a difference in shift for quaternary carbon, C-2, of 13.1 ppm and a mean ring carbon shift difference of 3.4 ppm. These data would indicate that the configuration of the side chain of **3** would place C-10 trans to C-1 as it is in **6**.[17] This configuration would also seem to be the most thermodynamically stable, as the forced 1,3 interaction energy between the hydrogen on bridgehead carbon C-1 and a substituent on C-9 would be lower for the small olefinic hydrogen atom than for the bulkier methylene group (C-10) of **3**.

The bridgehead carbon chemical shifts would be expected to differ significantly in compound **3** since C-1 is α to the olefinic linkage while C-4 is β. The shift difference ($\Delta\delta_{1-4}$ = 9.9 ppm) compares favorably with the bridgehead carbon shift difference for compound **6** (see Table I).

The ^1H NMR spectrum of **3** indicates the presence of the exocyclic double bond by the appearance of a distinct doublet at 3.5 ppm, representing the protons on C-10. The single olefinic proton appears as a broad multiplet, centered at 5.2 ppm.

The notable differences between the ^{13}C spectra of **2** and **3** are the positions of the olefinic carbons and the shifts of the two bridgehead carbons. Concerning the latter difference, a small separation in the shifts of these carbons in **2** is expected, considering their equivalent proximity to the double bond. The observed difference in shift for these two carbons in **2** compares favorably with the 4.2-ppm difference seen for comparable carbons in **8**. Likewise, all equivalent carbons in molecules **2** and **8** are within 0.6 ppm in chemical shift with the exception of those carbons which are α to the point of substitution.

The ^1H NMR of **2** gave the expected triplet at 3.1 ppm for the hydrogens α to the protonated amine. The olefinic proton at C-3 appeared as a pair of quartets at 6.1 ppm.

Experimental Section

All ^1H NMR spectra were run on a Varian 60-MHz EM-360 spectrometer with either Me_4Si or hexamethyldisiloxane as an internal reference. ^{13}C NMR spectra were run on a Varian CFT-20 spectrometer and are referenced to Me_4Si. Methyl, methylene, and methine assignments were determined by the single-frequency off-resonance decoupling (SFORD) technique. IR spectra were recorded on a Beckman IR-18A spectrophotometer and are referenced to polystyrene. Melting points were determined on a Mel-Temp or a Fisher-Johns melting point apparatus and are uncorrected.

Bicyclo[2.2.2]octan-2-ol (9). Hydroboration[19] of commercially available bicyclo[2.2.2]oct-2-ene was accomplished by reacting 1.0 equiv of the octene with 0.37 equiv of borane–methyl sulfide complex and 1.1 equiv of H_2O_2 in anhydrous ethyl ether. The pure alcohol, as white crystals, was recovered in 70% yield after purification by sublimation under vacuum; mp 215 °C (with sublimation) (lit.[20] mp 218.5 °C).

Bicyclo[2.2.2]octan-2-one (10). To 1.0 equiv of **9** in acetone was slowly added chromic acid oxidizing reagent[21] until an orange color persisted. After neutralization with $NaHCO_3$, the product was taken up in ether, dried over anhydrous $MgSO_4$, and sublimated under vacuum to give **10** as colorless crystals: 65–70% yield; mp 174–180 °C (lit.[20] mp 173–177 °C).

2-(Cyanomethyl)bicyclo[2.2.2]octan-2-ol (11). Cyanomethylation[22] of **10** was accomplished by adding 1.0 equiv of **10** to 1.0 equiv of CH_3CN and 1.1 equiv of *n*-butyllithium in freshly distilled, dry THF at −78 °C. The product was isolated as a thick yellow oil that was of sufficient purity for use in subsequent reactions. A 70% yield of **11** as white plates could be obtained by crystallization from ether/petroleum ether: mp 41–42 °C; ^1H NMR δ 2.63 (s, 2 H), 2.35 (s, 1 H), 1.63 (m, 12 H); IR ($CHCl_3$) 3560, 3450, 2240 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.73; H, 9.09; N, 8.48. Found: C, 72.60; H, 9.29; N, 8.31.

2-(2-Aminoethyl)bicyclo[2.2.2]octan-2-ol (1). Compound **1** was prepared by adding a solution of **11** in anhydrous ether to a 2.4 molar excess of $LiAlH_4$ in anhydrous ether under nitrogen and stirring the mixture at room temperature for 4 h.[23] After precipitation of the metal hydroxides by the successive addition of water and 5 N NaOH, **1** (in 70% yield) was isolated as off-white crystals. Further purification was accomplished by recrystallization from ether/petroleum ether, which gave **1** as a fine white powder: mp 100–101 °C; ^1H NMR δ 3.03 (t, 2 H), 2.78 (br s, 3 H), 1.41 (m, 14 H); IR ($CHCl_3$) 3380, 3240, 1570, 1450, 1165, 1075 cm^{-1}.

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Anal. Calcd for $C_{10}H_{19}NO$: C, 71.00; H, 11.24; N, 8.28. Found: C, 70.88; H, 11.07; N, 8.07.

2-(2-Aminoethyl)bicyclo[2.2.2]oct-2-ene Hydrobromide (2). A 250-mL, three-necked, round-bottomed flask was equipped with a nitrogen inlet and thermometer adapter and heated at 210 °C for 8–12 h. While cooling under dry nitrogen, a condensor with a line to an oil bubbler and a magnetic stirbar were added. The flask was charged with 100 mL of dry, freshly distilled *p*-xylene and 2.1 mmol (550 mg) of triphenylphosphine (99%). With vigorous stirring, under nitrogen, 1.9 mmol (0.1 mL) of bromine was added via micropipet, and a precipitate, presumably triphenylphosphine dibromide, formed. The mixture was heated to 80 °C to drive off any unreacted bromine and then cooled to 40 °C, at which time 1.9 mmol (328 mg) of 1 was added as a solid, and heating was reinitiated. When the reaction temperature reached 70–80 °C, a catalytic amount of hydroquinone was added, the flask covered to omit light, and heating continued to 115–125 °C. The evolution of HBr was monitored by moistened pH paper, and the reaction was allowed to heat until 30 min past the point where HBr could no longer be detected (approximately 2 h). The reaction was then cooled to room temperature, and the product, as the hydrobromide salt, was isolated by suction filtration and washed with benzene. The *p*-xylene was washed three times with water, and the aqueous phases were lyophilized. A 77.8% yield of crude endo- and exocyclic olefinic isomers was obtained. The isomers could be separated by repeated recrystallization from a methanol/ether solution. Pure **2** decomposed at 229–232 °C: ^{1}H NMR δ 6.1 (2 q, 1 H), 3.1 (t, 2 H), 2.43 (m, 4 H), 1.25 (m, 8 H); ^{13}C NMR, see Table I.

Anal. Calcd for $C_{10}H_{18}NBr$: C, 51.72; H, 7.76; N, 6.03; Br, 34.48. Found: C, 51.68; H, 7.90; N, 5.94; Br, 34.56.

2-(2-Aminoethylidene)bicyclo[2.2.2]octane Hydrobromide (3). A 250-mL three-necked flask, equipped and treated as above, was charged with 2.1 mmol of triphenylphosphine (99%) and 50 mL of bis(2-ethoxyethyl) ether. Bromine (0.1 mL) was added as previously described, and the mixture was heated to 50 °C. A solution of 1.9 mmol of **1** in 50 mL of solvent was added in a dropwise fashion. The remainder of the reaction proceeded as previously described. After the mixture cooled, a majority of the solvent was removed by distillation under vacuum. Benzene was added to the residue and, if the product precipitated, it was filtered and washed with benzene. In cases where precipitation did not occur, the organic phase was extracted three times with water and the water evaporated in vacuo. A 35% yield of crude **3** resulted. Purification was accomplished by recrystallization from a methanol/ether solution. Pure **3** decomposed at 222–225 °C: ^{1}H NMR δ 5.22 (m, 1 H), 3.56 (d, 2 H), 2.27 (m, 3 H), 1.56 (m, 9 H); ^{13}C NMR, see Table I.

Anal. Calcd for $C_{10}H_{18}NBr$: C, 51.72; H, 7.76; N, 6.03; Br, 34.48. Found: C, 51.63; H, 7.78; N, 5.97; Br, 34.36.

3-Bromo-2-[2-[[(*p*-methoxybenzyl)carbonyl]amino]ethyl]bicyclo[2.2.2]octane (5). The dehydrohalogenation reaction proceeded as described for the synthesis of **2**, only the protection from light and addition of hydroquinone steps were eliminated. The crude products were recrystallized from methanol/ether and dried. One gram of the mixed hydrobromides was allowed to stir in dry benzene at room temperature for 4 h with 1 mL of dry pyridine and 0.617 g of freshly distilled (*p*-methoxyphenyl)acetyl chloride, prepared in the standard manner from the acid and $SOCl_2$. The organic phase was washed consecutively with water, 10% HCl, 10% NH_4OH, and water and dried over anhydrous $MgSO_4$. The products were isolated as a medium yellow oil. A 10% aqueous neutral alumina column (2 × 40 cm) was prepared in hexane, and 400 mg of the product mixture was eluted with 250-mL aliquots of the following solvent mixtures in a nonpolar gradient: hexane/benzene, 4:1, 2:1, 1:1, 0:1; benzene/chloroform, 4:1, 2:1, 1:1, 0:1; chloroform/ether, 4:1, 3:1, 2:1, 1:1, 0:1. Fractions of 50 mL each were collected. Fractions 24–31 were combined and recrystallized twice from ether/petroleum ether to give approximately 50 mg of **5** as a white powder: mp 110–111 °C; ^{1}H NMR δ 4.17 (m, 1 H), 3.10 (t, 2 H), 3.76 (s, 3 H), 3.46 (s, 3 H), 5.43 (br, 1 H); IR (KBr) 1640, 1616, 1250, 1035 cm^{-1}; mass spectrum (ion block temperature 110–120 °C), *m/e* 379, 381 (m^+), 299 (m^+ – HBr), 82 ($H^{81}Br$), 80 ($H^{79}Br$).

Anal. Calcd for $C_{19}H_{26}NO_2Br$: C, 60.00; H, 6.84; N, 3.68; Br, 21.05. Found: C, 60.20; H, 7.00; N, 3.68; Br, 20.90.

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Registry No. **1**, 80641-34-5; **2**, 80641-35-6; **3**, 80641-36-7; **5**, 80641-37-8; **6**, 53844-99-8; **7**, 53845-00-4; **8**, 4893-13-4; **9**, 18684-63-4; **10**, 5019-82-9; **11**, 80641-38-9; bicyclo[2.2.2]oct-2-ene, 931-64-6; acetonitrile, 75-05-8; (*p*-methyoxyphenyl)acetyl chloride, 4693-91-8.

Communications

Total Synthesis of Carbohydrates: Stereoselective Syntheses of 2,6-Dideoxy-D-*arabino*-hexose and 2,6-Dideoxy-D-*ribo*-hexose

Summary: Short, highly stereoselective syntheses of the title carbohydrates from allylic alcohol precursors are described. A synthesis of the racemic *arabino*-deoxyhexose is also described. These syntheses feature the highly regioselective epoxide ring opening reactions of intermediates **7**, **11**, and **12** and the asymmetric epoxidation–kinetic resolution of allylic alcohol **10**.

Sir: In connection with a synthesis of olivomycin A (**1**)[1] we require access to a number of dideoxy and branched-chain sugars.[2] Syntheses of the requisite monosaccharides starting from available hexoses have been reported, but in some cases the routes require many synthetic transformations.[2a,3] This problem is frequently encountered in syntheses which originate from carbohydrate "chiral pool" precursors.[4] On the other hand, chemical syntheses

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