precursors to alkoxy radical spin adducts for structure confirmation.

Experimental Section

Instrumentation. ESR spectra were recorded on a Varian E-4 spectrometer equipped with a Varian temperature control unit. Spectra were calibrated by using the stable nitroxide 3-carbamoyl-2,2,5,5-tetramethyl-3-pyrrolin-1-yloxy (Aldrich). ^{1}H and ^{13}C NMR spectra were recorded at 30 and 75.47 MHz, respectively.

Spin-Trapping Procedure. Solutions of the nitrones were generated from the hydrotriflate salts by TLC on silica gel plates (Merck) using 9:1 CH_2Cl_2–MeOH solvent as previously described.[7] In a typical experiment a millimolar benzene solution of the α-alkoxynitrone was deoxygenated with argon for 20 min at which time a small amount of the radical source was added. The solutions were then irradiated in the cavity of the spectrometer by using a Spectroline low pressure mercury vapor lamp.

Kinetic Procedure. The α-alkoxynitrone solution was generated as above and its concentration determined by UV absorbance. In this manner, a solution containing both traps at millimolar concentrations was prepared and deoxygenated with argon. For kinetic runs, the temperature of the cavity was maintained at 25.0 ± 0.2 °C. Identical spectrometer settings, cells, and lamp position were used for each experiment. After computer simulation of each spectrum, the program of Oehler and Janzen[10] gave the relative peak areas used in kinetic plots. The relative rate ratios reported are an average of five kinetic experiments for each nitrone.

UV extinction coefficients of α-alkoxynitrones were measured in benzene: **3a**, λ_{max} 321 (ϵ 11 000); **3b**, λ_{max} 319 (ϵ 17 500); **3c**, λ_{max} 393 (ϵ 11 000). Concentrations of the α-alkoxynitrones for this purpose were determined by integration of NMR signals of the α-alkoxynitrone and an internal standard of known concentration.

Acknowledgment. This research was supported by an NSF Chemical Instrumentation Grant CHE-8406088, and equipment grant from the W. M. Keck Foundation, and fellowships from the ARCS Foundation. We also thank Drs. Henry N. Blount and Peter L. Gutierrez for helpful discussions.

Registry No. **1**, 3376-24-7; **3a**, 118949-64-7; **3b**, 118949-65-8; **3c**, 118949-66-9; **4**, 118949-68-1; **5**, 21999-41-7; Bu_3SnH, 688-73-3; Me_4Sn, 594-27-4; Bu_4Pb, 1920-90-7; Bu_4Sn, 1461-25-2; $PhPb(OAC)_3$, 3076-54-8; Ph(MeO)CHN(O$^\bullet$)Bu-*t*, 34234-86-1; Ph(EtO)CHN(O$^\bullet$)Bu-*t*, 34280-35-8; Ph_2(MeO)CN(O$^\bullet$)Bu-*t*, 118949-70-5; 4-$O_2NC_6H_4$(Bu)C(OMe)N(O$^\bullet$)Bu-*t*, 118949-71-6; 4-$MeOC_6H_4$(Bu)C(OMe)N(O$^\bullet$)Bu-*t*, 118949-72-7; Ph(MeO)C(Me)N(O$^\bullet$)Bu-*t*, 118949-73-8; α-ethoxy-α-phenyl-*N*-*tert*-butylnitrone, 118949-67-0; α-methoxy-α-methyl-*N*-*tert*-butylnitrone, 118949-69-2; phenylazotriphenylmethane, 981-18-0; phenylmercuric chloride, 100-56-1.

Theoretical (MM2) Conformational Analysis of 1,4-Dioxepane

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Introduction

Molecular mechanics calculations have proven to be very useful in molecular dynamics studies for organic compounds.[1] The pseudorotational equilibria in seven-membered rings have already been studied by different force field methods. Cycloheptane itself, **1**, was studied by Hendrickson,[2] and the twist-chair (TC) conformation was found to be the most stable. These results were confirmed by Bocian[3] and, more recently, by Ōsawa[4] who used MM2′,[5] a modification of Allinger's force field.[6] Bocian[7] also studied 1,3-dioxepane, **2**, finding a TC conformation again as the most stable. Recently, Kamalov[8] has carried out a theoretical study on the conformational transitions for this compound, confirming Bocian's results. In contrast, 1,4-dioxepane, **3**, has not been conformationally studied, although related compounds 1,5-benzodioxepins, **4**, have been experimentally studied (NMR)[9] and show preference for chair (C) or twist-boat (TB) conformations, depending on the substituents on C-3. In this paper we described the MM2 results on the conformational analysis of **3**.

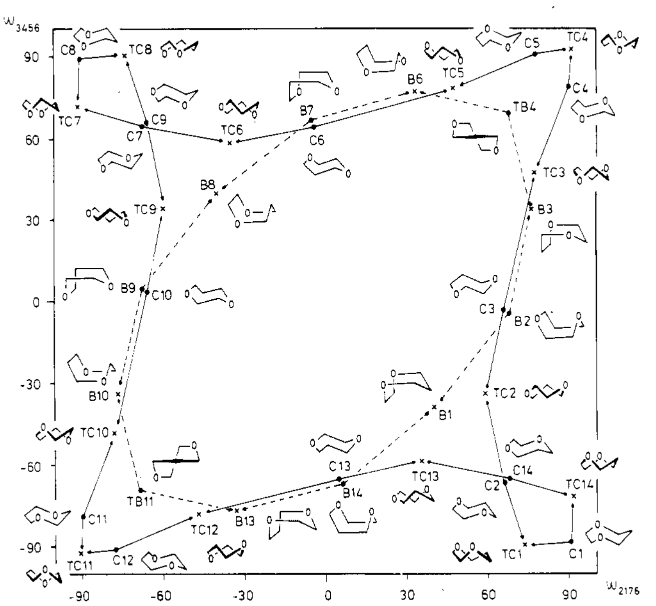
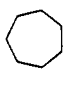


Figure 1. Schematic representation of the T/TC and B/TB pseudorotational pathways as a function of the two internal dihedral angles ω(2176) and ω(3456). Points represent saddle points while x represent energy minima.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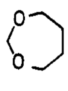
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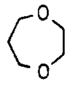
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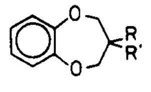
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Results and Discussion

The conformational analysis has been carried out in two well-defined steps: (i) calculation of the torsional energy

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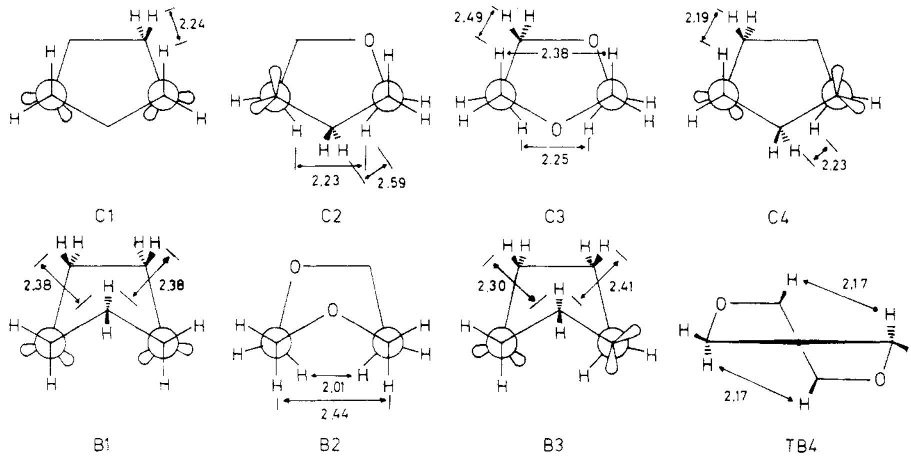

Figure 2. Nonbonding hydrogen interactions present in C1, C2, C3, C4, B1, B2, B3, and TB4 conformations of 3.

surface representing the pseudorotational movement of the studied family by using either the one- or two-bond drive technique within MM2 program and (ii) full characterization of the stationary points by using a BIGSTRN-3 program[10] implemented with all MM2 parameters. After locating one-dimensional energy maxima, the eigenvector distortion option included into the BIGSTRN-3 program was applied for obtaining the energy minima connected by the maxima.[11]

Both conformational families for cycloheptane have been considered in this study: the chair/twist-chair (C/TC) and the boat/twist-boat (B/TB), the former being less energetic than the later.

Chair/Twist-Chair Family. The C/TC family contains 14 chair (C1, C2, ..., C14), and 14 twist-chair (TC1, TC2, ..., TC14) conformations (Figure 1). Conformation C1 is defined as that having plane of symmetry and the C-6 above an hypothetical equatorial molecular plane. The pseudorotational pathway has been established starting at C1 and following a clockwise movement. Chair conformations are energy maxima and twist-chairs are energy minima located between chairs.

The schematic representation of the pseudorotational pathway as a function of two internal dihedral angles (ω(2176) and ω(3456)) is shown in Figure 1. Only four chair and four twist-chair conformations are energetically unique, with TC3, TC5, TC10, and TC12 as the most stable ones.

The smaller stability of chair conformations compared to twist-chair can be rationalized, as in cycloheptane, considering the nonbonding interactions between the transannular hydrogen atoms. The main nonbonding distances existing in C1, C2, C3, and C4 are shown in Figure 2.

Four types of important interactions can be observed between the H atoms of 3: (i) H/H-1,2-syn diaxial interaction in C1 and C4, similar to that of 1; (ii) H/H-1,3-syn diaxial interaction in C3 (2.49 Å), also comparable to that of 1; (iii) H/H-1,3-syn$_{O}$diaxial interaction in C1, C3, and C4, i.e., between diaxial H atoms on carbons separated by an oxygen atom, and (iv) H/H-1,4-transannular interaction in C2 and C3. The two latter interactions are stronger than the corresponding one in 1 as a consequence of the shorter C–O compared to C–C bond length, which produces also short H/H nonbonding distances (2.23 Å in C1, C2, and C4, 2.25 Å in C3, and 2.38 Å in C3). All these interactions substantially relax when twisting chair conformations.

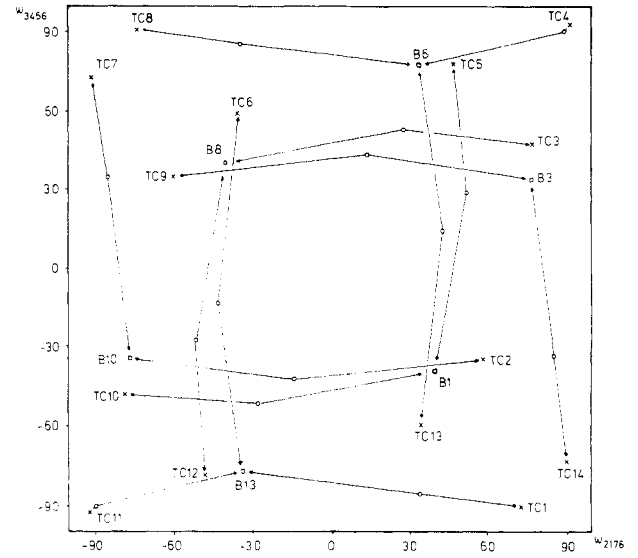

Figure 3. Schematic representation of the interconversion processes between TC and B conformers as a function of the two internal dihedral angles ω(2176) and ω(3456). TC conformers are represented by x, B conformers by squares, and the saddle points by open circles.

Boat/Twist-Boat Family. This family should, as in the case of 1 and 2, contain 14 boat and 14 twist-boat conformations starting at B1, which can be obtained from C1 by moving C-6 from above to below the equatorial plane. As in the parent compound, cycloheptane, the twist-boat conformations are expected to be energy minima.

The conformational behavior of 3 has been hardly surprising regarding the B/TB family, at least under MM2 force field. Only six energy minima between only six energy maxima complete the pseudorotational pathway. The schematic representation of the energy surface as a function of two internal dihedral angles (ω(2176) and ω(3456)) is also shown in Figure 1.

A careful geometrical analysis of those stationary points indicates boat conformations (B1, B3, B6, B8, B10, and B13) as the energy minima while four of the transition states are boat (B2, B7, B9, and B14) and the other two are twist-boat conformations (TB4 and TB11). Conform-

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[10] Nachbar, R. B., Jr.; Mislow, K. Available in QCPE program no. 514, and described in *QCPE Bulletin* **1986**, *6*, 96.

[11] BIGSTRN-3 program allows to use four types of optimization procedure. In step ii a full-matrix Newton–Raphson optimization was used, while the eigenvector distortion was carried out by variable metric optimization.

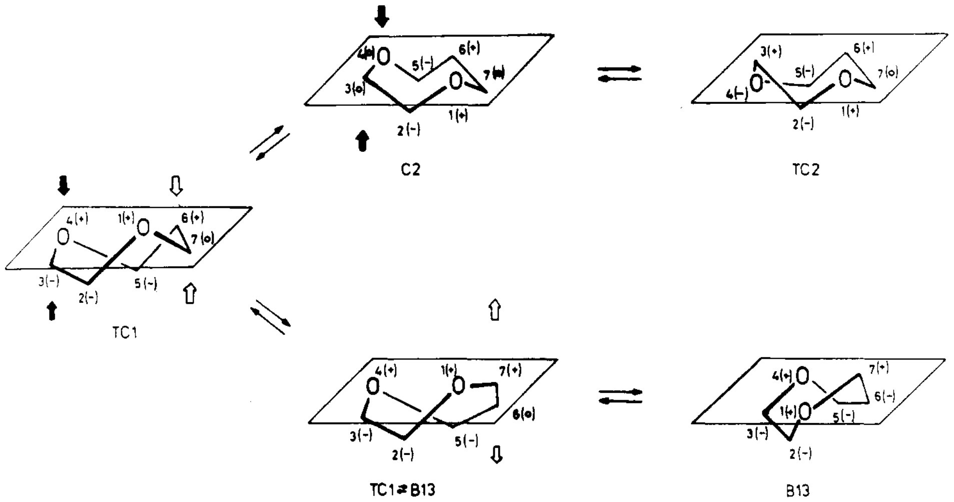

Figure 4. Interconversion of TC1 into TC2 and B13. Signs represent the atomic location above (+) or below (−) an hypothetical equatorial molecular plane. Arrows denote main atomic movements for the TC1 $\rightleftharpoons$ TC2 (solid) and for the TC1 $\rightleftharpoons$ B13 (open) interconversion processes.

ers B1 and B8 are isoenergetic (3.87 kcal/mol relative to TC3) and B3, B6, B10, and B13 have also the same energy (3.82 kcal/mol). The energy maxima present a similar situation, too: B2, B7, B9, and B14 are 5.02 kcal/mol higher in energy than TC3, while TB4 and TB11 are the most energetic transition states (6.03 kcal/mol).

The stability difference among boat conformers, and the high energy contents of the two twist-boat conformations, as well as the absence of any other conformation in this family can be explained considering the nonbonding interactions between H atoms. Figure 2 contains the more representative nonbonding distances between H atoms in the B1, B2, B3, and TB4 conformations.

Conformations B1 and B3 present two types of strong interactions: (i) H/H-1,2-syn diaxial between H at C-2 and C-3 (B1), and at C-5 and C-6 (B3) and (ii) H/H-1,4-transannular between the H atoms separated 2.38 Å in B1 and 2.30 and 2.41 Å in B3. The small energy difference between B1 and B3 cannot be easily attributable to a single cause. Twisting these boat conformations does not reduce the energy since an approaching of the H at C-2 or C-3 and those at C-6 in B1, and H at C-5 or C-6 and those at C-2 in B3 is produced. This approaching destabilizes twist-boat conformers and makes B1 and B3 energy minima in the pseudorotational equilibria. The high energy contents of B2 can be justified considering two strong interactions: (i) H/H-1,3-syn$_{O}$diaxial and (ii) H/H-1,4-transannular. Twisting of B2 diminishes these interactions making, then, B2 the transition state for the interconversion B1 $\rightleftharpoons$ B3.

The existence of a twist-boat conformation (TB4 or TB11) as a transition state can be rationalized considering the presence of two strong H/H-1,4-transannular interactions between H atoms at 2.17 Å. The twisting of TB4 (or TB11) going to B4 or to B5 increases one of these interactions while releases the other, and if the twisting proceeds further than B4 or B5 the release of the second interaction happens. All this converts B4 and B5 into nonstationary conformations on intermediate positions between B3 and TB4 or TB4 and B6, respectively.

The energy difference between C/TC and B/TB families seems to be due to an increase in the nonbonding interactions. Thus, atoms C-2 (or C-3) and C-6 have considerably approached in B1 as compared to C1. Moreover, oxygens O-1 and O-4 have also approached each other in B1 (2.76 Å and 2.64 Å in C1 and B1, respectively), although this interaction requires less energy than the previous one. In contrast, the H nonbonding interaction balance favors B1 since two strong H/H-1,3-syn$_{O}$diaxial contacts in C1 have been substituted by two H/H-1,4-transannular interactions with H atoms at 2.38 Å in B1. This behavior seems to be general among both families.

Interconversion between C/TC and B/TB Families. The interconversion between both families has also been studied and is represented in Figure 3 as a function of the two internal dihedral angles $\omega(2176)$ and $\omega(3456)$. The representation of pseudorotational movements among each family has two planes of symmetry, while the C/TC $\rightleftharpoons$ B/TB interconversion shows an S_2 axis.

There is no numerical correlation between boat and chair conformations as a consequence of two factors: the numbering of boats and chairs is not related, and the number of minima in each family is much too different (14 for the C/TC and only six for the B/TB), producing that two different TC conformers transform into the same B conformer passing through geometrically different transition states.

Only four energetically different transitions are possible, the representative of them being: TC1 $\rightleftharpoons$ B13 (7.50 kcal/mol), TC2 $\rightleftharpoons$ B10 (10.71 kcal/mol), TC3 $\rightleftharpoons$ B8 (10.11 kcal/mol), and TC4 $\rightleftharpoons$ B6 (7.96 kcal/mol). The least energetic represents the change from TC1 to B13 (or TC7 to B10, or TC8 to B6, or TC14 to B3). Each energetically different transition state group has four geometrically distinct conformations, but one group has only two showing C_2 axes of symmetry.[12]

The ring-angle deformation seems to be the main factor producing their energy differences. When one TC conformation, i.e. TC1, transforms into another (TC2), two adjacent atoms interchange their positions relative to the hypothetical equatorial molecular plane (Figure 4) with almost no change in the ring bond angles. However, when TC1 transforms into B13, two other adjacent atoms move, leading to a transition state where five atoms are almost in the same plane ($\omega(1765) = 14°$ and $\omega(2176) = 22°$). This movement produces large deformations in the ring bond angles, especially in those centered at the moving atoms.

The intraannular bond angles showing the larger deviations from MM2 natural values in the less energetic

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[12] The eigenvector distortion of the saddle point TC4 $\rightleftharpoons$ B6 by variable metric optimization connects TC4 and B6. However, distortion using a Newton–Raphson procedure makes this transition state to fall into TB4, which, in turn, is the transition state between B3 and B6 in the B/TB pseudorotational pathway. No connection between TC4 and B3 has been found.

transition state, TC1 $\rightleftharpoons$ B13, are those centered at C-6 and C-7, while the highest transition state, TC2 $\rightleftharpoons$ B10, presents large deviations at angles centered at C-7 and O-1. The relative energy among transition states is a consequence of the bond angle type suffering the largest deformation. Modification of an angle of C–C–C type requires less energy than that of one of C–C–O type, and both need less energy than deformation of one of C–O–C type due to both their natural bond angle and bending constants in the MM2 force field (109.5°, 107.4°, and 106.8°, and 0.45, 0.70, and 0.77 mdynes Å/rad, respectively).

Conclusions

The conformational dynamics of 1,4-dioxepane, **3**, has been fully studied by MM2 calculations. The compound shows twist-chair conformations (TC3, TC5, TC10, and TC12) in its ground state and pseudorotates within the C/TC family less freely than its parent hydrocarbon, cycloheptane **1**. The B/TB family of **3** presents two main peculiarities: (i) some B conformations are energy minima and two TB are energy maxima while B are maxima and TB minima in **1**, and (ii) only 12 stationary points (six maxima and six minima) compose its pseudorotational pathway. The interconversion between C/TC and B/TB families has also been studied and a barrier of 7.5 kcal/mol found.

Registry No. 1,4-Dioxepane, 505-68-0.

Supplementary Material Available: Tables containing the internal dihedral angles and relative energies for the stationary points of the conformational pathways of **3** and table containing the intraannular bond angles for the energetically unique transition states between C/TC and B/TB families as well as their deviation from the MM2 natural values (4 pages). Ordering information is given on any current masthead page.

A Short Synthesis of (±)-Gephyrotoxin 223AB

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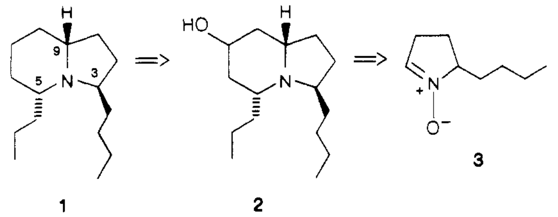
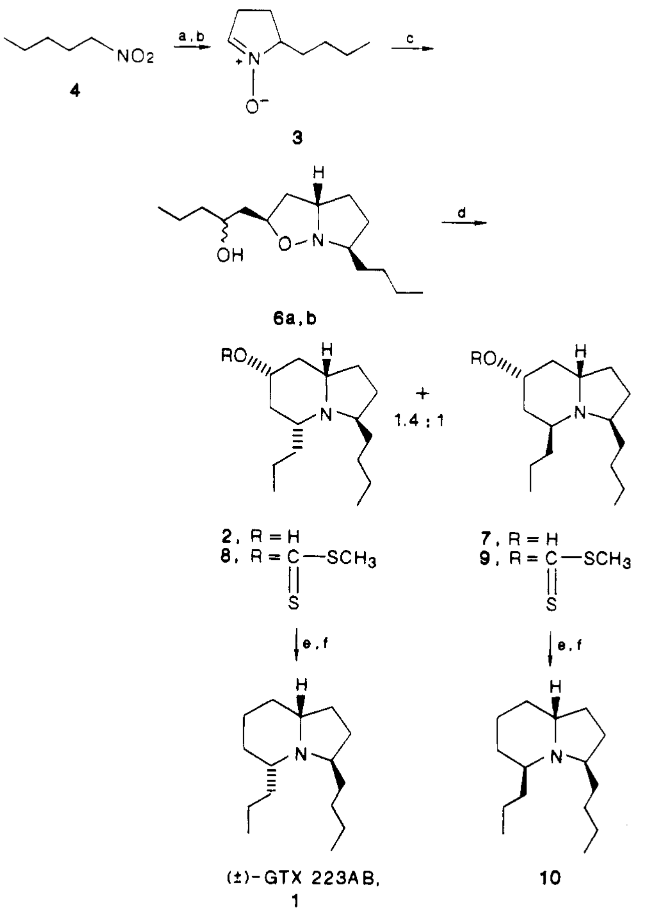
Bicyclic Gephyrotoxin 223AB (**1**), an alkaloid found in the skins of brightly colored Central and South American frogs of the genus *Dendrobates*,[1-3] has attracted wide interest in the last few years because of its promising pharmacological activity. These indolizidine and related compounds "probably represent a structural class of noncompetitive blockers of neuromuscular transmission".[4] This interest has resulted in a few syntheses of **1**,[5] also in its enantiomeric natural (–) form,[6] and in the syntheses of stereoisomers of **1**.[7]

We report now a new short and efficient synthesis of (±)-GTX 223AB (**1**), based upon a 1,3-dipolar cycloaddition of a cyclic nitrone with complete stereochemical control. Our synthesis is characterized by a very short number of steps and by the fact that only one separation of isomers is required and can be executed before the final step on stable materials that are easier to handle.

Scheme I



Scheme II[a]



[a] (a) NaOMe/MeOH, $H_2C{=}CHCHO$, 0 °C, 57%; (b) 4-nitrooctane aldehyde (**5**), Zn/AcOH, 5 °C, 51%; (c) 4-hydroxyheptene, 110 °C, 46 h, 61%; (d) (i) MsCl, Py; (ii) H_2/Pd/C 10%, 57 h, 67%; (e) NaH, CS_2, MeI, 67 °C, 84%; (f) Bu_3SnH, AIBN, 110 °C.

We focused on the alcohol **2** as a suitable intermediate, containing the right relative 5*E*,9*E* stereochemistry, from which the GTX 223AB can be obtained by known reactions, without affecting the chiral centers. Compound **2** is easily accessible from a functionalized isoxazolidine[8]

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