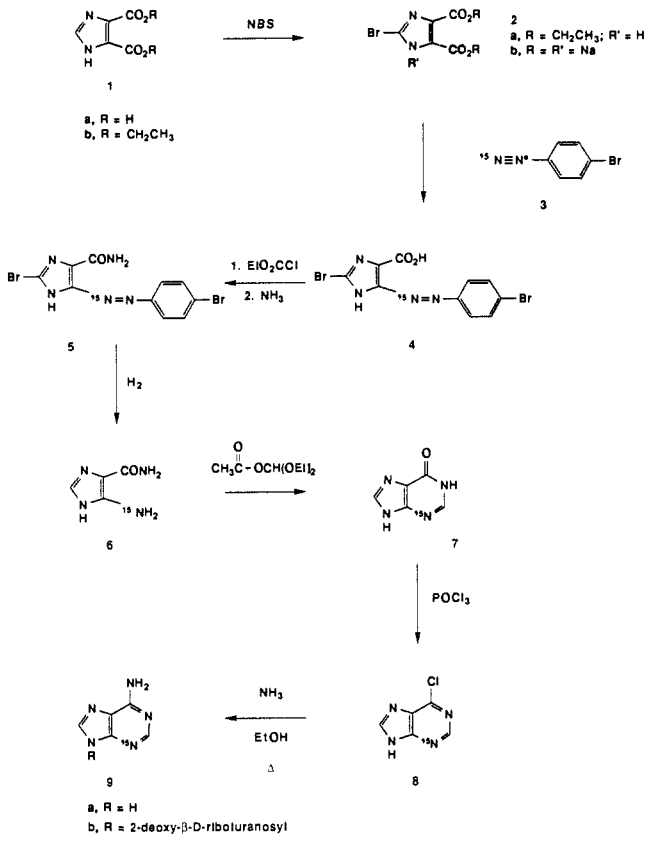
Scheme I



using diethoxymethyl acetate. This reaction was carried out in DMF for 3 h at reflux. After evaporation of solvents, but without additional purification, **7** was then converted to [3-^{15}N]-6-chloropurine (**8**) by reaction with $POCl_3$ and dimethylaniline.[26] The overall yield from **5** was 72%. The amination of **8** to [3-^{15}N]-adenine (**9a**) was effected by using ethanolic ammonia in a bomb at 120 °C. The crude **9a** contains some ammonium chloride, but it can be used directly for glycosylation without further purification. The glycosylation reaction was carried out by enzymatic transglycosylation using thymidine, thymidine phosphorylase, and purine nucleoside phosphorylase,[27,28] as we had done for synthesis of [7-^{15}N]-labeled deoxynucleosides.[24] The overall yield was 46% from **5** or 64% from **8**.

This route is an overall highly efficient synthesis of [3-^{15}N]-adenine and [3-^{15}N]-2'-deoxyadenosine. The reactions employed are generally high yield and require minimal purification procedures. The labeled ribonucleoside is also available by this route simply by using uridine as the glycosyl donor in the enzymatic transglycosylation reaction rather than thymidine.[27,28] Moreover, the [5-^{15}N]-AICA intermediate (**6**) is a useful precursor for [3-^{15}N]-labeled guanine and isoguanine derivatives.[19,20] Thus this route provides formal entry into [3-^{15}N]-labeled nucleosides of both the adenine and guanine families.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM31483) and the Busch Memorial Fund and an American Cancer Society Faculty Research Award to R.A.J.

Supplementary Material Available: A complete experimental section for compounds **1b–9b** (5 pages). Ordering information is given on any current masthead page.

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Chirality Transmission Involving a Free-Radical-Mediated 6-Exo Cyclization Process. Stereocontrolled Synthesis of Branched-Chain 1,4-Diols

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Drawing upon the vast wealth of information accumulated on free-radical-mediated cyclization reactions, organic chemists have effectively exploited the well-documented overwhelming predilection for the 5-exo mode of cyclization of the 5-hexenyl radicals and their equivalents over the corresponding 6-endo pathway.[1] A notable exception to this general rule includes the reaction of the 2-sila- and 2-sila-3-oxahexenyl radicals where the 6-endo mode of cyclization becomes competitive[2-4] or, with certain olefin structures, predominant.[5] In contrast, there has been much less investigative focus on the use of the 6-heptenyl radical or its equivalent in regio- and stereoselective synthesis.[6] In connection with our synthetic study of the plant hormone brassinolides, we became interested in the intramolecular cyclization of the 2-sila-3-oxa-6-heptenyl radicals (**1**) which do not carry electron-withdrawing groups at the distal olefinic carbon (Scheme I). Interestingly, the results obtained by Nishiyama and co-workers show only marginal acyclic regio- and stereoselectivity in the 5-exo and/or 6-endo cyclizations of the radicals generated from several (bromomethyl)dimethylsilyl allyl ethers.[3] We report herein that radicals **1** (R^1 = H, R^2 = Me, and R^1 = R^2 = Me) undergo highly regio- and stereoselective 6-exo-mode cyclization (pathway a, Scheme I) to produce six-membered siloxanes, which upon oxidation afford branched-chain 1,4-diols. This formally constitutes a net syn-selective reductive hydroxymethylation of chiral homoallylic alcohols.

The requisite (bromomethyl)silyl ethers were obtained in quantitative yield from their corresponding homoallylic alcohols with (bromomethyl)dimethylsilyl chloride/Et_3N in CH_2Cl_2 (0 °C, 2-3 h). Cyclization was then effected with (*n*-Bu)$_3$SnH, generated in situ from a catalytic amount of (*n*-Bu)$_3$SnCl and an excess of $NaB(CN)H_3$,[7] in refluxing *t*-BuOH (12-16 h) in the presence of a catalytic amount of AIBN. The cyclic siloxanes thus obtained were smoothly converted into the corresponding diols by treatment with excess 30% H_2O_2/$KHCO_3$ in refluxing THF/MeOH (2-3 h).[8] As summarized in Table I, the radicals generated from the (bromomethyl)silyl ethers with mono- or dimethyl-substituted olefins (entries 2, 3, 5, and 7) underwent regioselective 6-exo-mode cyclization to produce exclusively the six-membered *cis*-siloxanes in 89-98% yield (see pathway a in Scheme I). The cis stereochemistry of these disubstituted siloxanes was ascertained through

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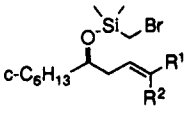
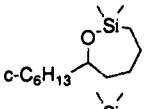
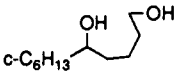
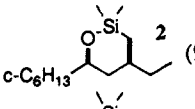
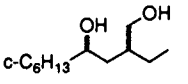
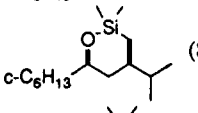
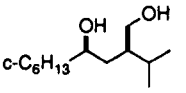
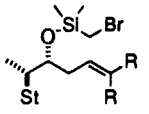
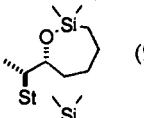
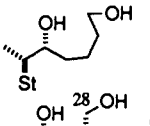
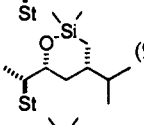
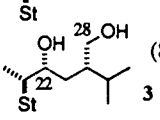
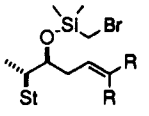
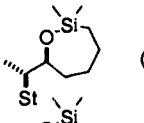
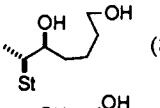
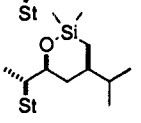
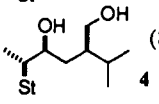
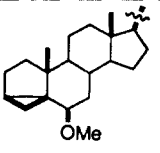
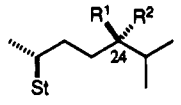
Table I. Cyclizations of the Radicals Generated from (Bromomethyl)silyl Ethers and Oxidations of Cyclic Siloxanes into Diols

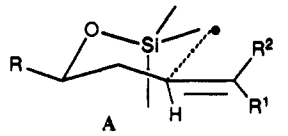
entry	bromomethylsilyl ether		siloxane	(% yield)[a]	diol	(% yield)[a]
1		$R^1 = R^2 = H$		(92)		(87)
2		$R^1 = H, R^2 = Me$		(90)		(85)
3		$R^1 = R^2 = Me$		(89)		(83)
4[b]		R = H		(95)		(80)
5[b]		R = Me		(95)		(87)
6[b]		R = H		(90)		(80)
7[b]		R = Me		(98)		(85)

[a] Yield of isolated, chromatographically homogeneous products. [b] St ≡ 

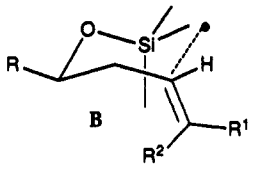
analysis of their 300- or 500-MHz ^1H NMR spectra in $CDCl_3$. Thus, as illustrated in Figure 1 for **2**, the proton–proton coupling constants observed for protons at C-3 and C-6 clearly indicate that the two substituents adopt equatorial orientations on the chair-like siloxane ring skeleton. The utility of this regio- and stereoselective synthesis of branched-chain 1,4-diols was further demonstrated by the synthesis of the 24-epimers of 28-hydroxylated steroids **5** and **6**, which are the key intermediates



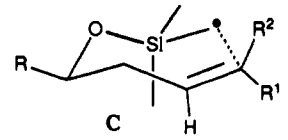
5 $R^1 = H; R^2 = CH_2OH$
6 $R^1 = CH_2OH; R^2 = H$



A



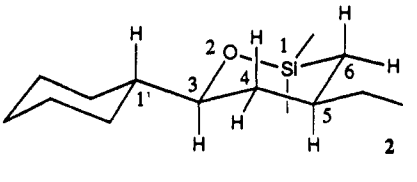
B



C

for the synthesis of a variety of natural steroids;[9] diols **3** and **4** were converted into 28-hydroxy steroids **5** (73%) and **6** (78%), respectively, in four steps: (1) selective protection of the 28-hydroxyl group with TBDMSCl (2.2 equiv), NEt_3 (1.5 equiv), DMAP (catalytic)/CH_2Cl_2, room temperature, 24 h;[10] (2) PhOC(=S)Cl (2.0 equiv)/pyridine/CH_2Cl_2, DMAP (catalytic), 0 °C–room temperature, 8 h; (3) $(n\text{-}Bu)_3SnH$ (1.5 equiv), AIBN (catalytic), toluene, reflux, 24 h; (4) TBAF (1.1 equiv)/THF, room temperature, 12 h. Somewhat unexpectedly, a complete reversal of regioselectivity was observed in the cyclizations of radicals lacking substitution at the olefin terminus (entries 1, 4, and 6), which provided exclusively the products of the 7-endo cyclization process (see pathway b in Scheme I).

The literature examples on the cyclization of α-silyl radicals seem to support the notion that these cyclizations are irreversible despite the enhanced stability of the radicals due to the presence of the silicon atom.[2] In addition, a recent report on the cyclization of the radical generated from a (bromomethyl)dimethylsilyl ether describes the stereoselective formation of the thermodynamically less stable ring system.[11] Therefore, the selectivity described above may be rationalized in terms of the relative stabilities of the three transition states A, B, and C which accommodate roughly the 107–109° approach angle of the radical onto the sp^2 center.[12] The syn selectivity of the 6-exo cyclization process may be ascribed to the less favorable pseudo-axial orientation of the olefinic group, particularly the steric effect of the R^2 group, in the transition state B. The 7-endo cyclization may be considerably impeded for the radicals with the methyl-substituted olefins due to the steric crowding upon approach of the radical onto the sp^2 center. However, the clear-cut reversal in the regioselectivity to favor the 7-endo cyclization of the radicals for the olefins without methyl substitution at the terminal olefinic carbon indicates apparent



$J_{3,4ax} = 11.1$ Hz
$J_{3,4eq} = 1.6$ Hz
$J_{3,1'} = 5.5$ Hz
$J_{4eq,5ax} = 2.1$ Hz
$J_{4eq,6eq} = 2.1$ Hz
$J_{5,6ax} = 13.3$ Hz
$J_{5,6eq} = 3.5$ Hz
$J_{6ax,6eq} = 14.0$ Hz

Figure 1. H–H coupling constants (500 MHz, $CDCl_3$).

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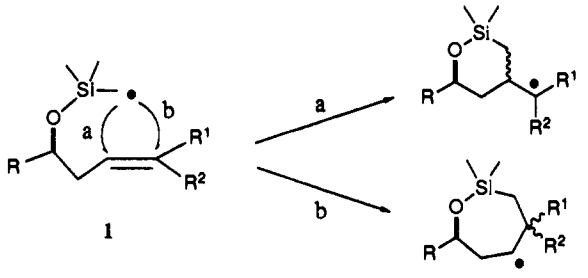
Scheme I



relative stability of the transition state C over A or B.

The high degree of regio- and stereocontrol demonstrated in this novel type of free-radical-mediated chirality transmission process in nonrigid, acyclic systems suggests the suitability of this approach as a general method for the hydroxy-directed 1,3-asymmetric induction at an sp^2 center. The stereoselective 6-exo α-silyl radical cyclization in combination with the facility of subsequent oxidative cleavage allows convenient access to branched-chain 1,4-diols.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. DK30025).

Supplementary Material Available: Complete spectroscopic characterization of all new compounds described in this paper including IR and ^1H and ^{13}C NMR spectral data and combustion and/or high-resolution mass spectral analyses of the molecular formula (13 pages). Ordering information is given on any current masthead page.

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Stereochemically Controlled Ligands Influence Atropisomerization of Pt(II) Nucleotide Complexes. Evidence for Head-to-Head and Stable Λ Head-to-Tail Atropisomers

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Received May 4, 1990

The remarkable effectiveness of Pt(II) anticancer drugs containing cis amines has prompted studies that demonstrate the need for at least one NH on each amine for reasonable activity.[1] The role such NH groups play in drug binding to DNA, the likely molecular target, is a central issue.[2] The drugs selectively cross-link adjacent guanine (G) residues by the N7s.[3] Selective

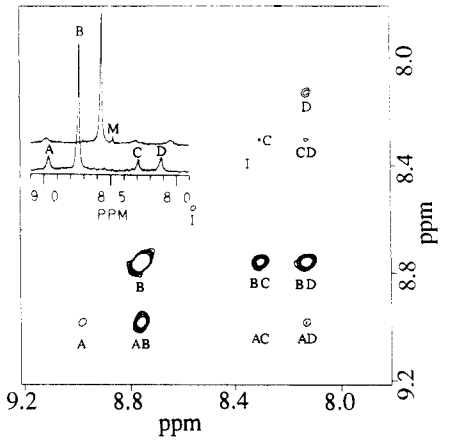

Figure 1. 2D EXSY spectrum (360 MHz, 22 °C, 360 ms mixing time, pH 3) of the products formed in a solution of 5′-GMP/(*R,S,S,R*)-LPt = 2:1. A, D, B, and C are H8 signals for HH, HH, HT(major), and HT(minor), respectively, in both 2D and 1D (insert) spectra. In the 2D spectrum, A is less intense than D as a result of magnetization transfer to NCH_3. Cross peaks are denoted by two letters. Insert: The upper spectrum in the insert is from the analogous (*S,R,R,S*)-LPt experiment. Minor peaks: M, residual 1:1 complex; I, minor impurities or noise.

binding of coordinating agents to target biomolecules and the contributions of H-bonding and steric effects in such binding are fundamentally important subjects.

X-ray and NMR studies of Pt oligonucleotide adducts with adjacent G residues cross-linked at N7 reveal that the two six-membered rings are on the same side of the Pt coordination plane (head-to-head, HH, conformation).[4] In the solid state, the large majority of cis bis complexes of 6-oxopurine bases, nucleosides, and nucleotides with several metal centers adopt the head-to-tail (HT) conformation, with the six-membered rings on opposite sides of this plane.[5] In only four cases, all from Lippert's laboratory and all Pt(II) complexes with 9-ethylguanine, was an HH conformation found.[5a]

In solution, *cis*-$[PtA_2(\text{nucleos(t)ide})_2]^{x(+\text{or}-)}$ complexes (where A = an amine or one-half of a diamine chelate) usually exhibit free rotation about the Pt–N7 bond.[6-9] In a pioneering study, Cramer demonstrated that guanosine rotation can be slowed sufficiently to detect atropisomers on the NMR time scale, if A_2

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‡ Università degli Studi di Bari.

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