will be disclosed in a full account of this work. Evidence for the covalent alkylation of DNA by the CBI-based agents was obtained from the thermally-induced strand cleavage of double-stranded DNA after exposure to the agents (autofootprinting),[9] Figure 1 (Supplementary Material). The autofootprinting was carried out with a 5′-end labeled fragment of SV40 (144 bp fragment, bp 138–5238) cloned into the Sma I site of the M13mp10 polylinker region [Agent:DNA incubation at 4 °C, 24 h; removal of unreacted agent through ethanol precipitation of DNA; thermal cleavage at 100 °C, 30 min].[24] Gel electrophoresis and autoradiographic evaluation of the DNA revealed that the observed sites of covalent alkylation and their relative intensities for CBI, **4**, **5**, and (+)-CC-1065 are identical.

The identical DNA binding properties of (±)-CBI-CDPI$_2$ (**5**) and (+)-CC-1065 (**1**) and their equipotent cytotoxic activity [IC_{50} (10^{-5} μg/mL), L1210: 1.2 (**1**) and 1.3 (**5**), B16: 1.4 (**1**) and 1.6 (**5**)] establishes that CBI-CDPI$_2$ constitutes an equivalent functional analogue of (+)-CC-1065 that embodies the fundamental and precise functional features of the agent responsible for its properties. Additional studies on the CBI-based agents will be disclosed in due course.

Acknowledgment. This work was assisted through the financial support of the National Institutes of Health (D.L.B., CA 41986; P.A.K., ES 03651), the Alfred P. Sloan Foundation, and American Cyanamid. We thank Dr. B. J. Invergo for early experimental contributions to this work.

Supplementary Material Available: Full physical and spectroscopic characterization of **3–5**, **6–13**, **17**, and **18**, a table of the full comparative properties of the CBI and CPI agents (Table I), additional details of the computational studies (eq 1), descriptive experimental and a summary of a series of autofootprinting studies (Figure 1), and a figure (Figure 2) representing the binding of (+)-CBI-CDPI$_2$ within a high affinity SV40 DNA binding site (15 pages). Ordering information is given on any current masthead page.

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(24) A summary of the autofootprinting study is provided as Supplementary Material.

Samarium(II) Iodide Mediated Transformation of Carbohydrates to Carbocycles

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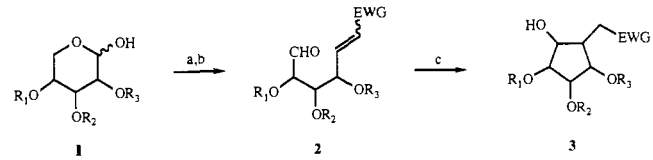
Recently, there has been considerable interest in the construction of carbocycles from carbohydrates with many of these reactions involving the cyclization of 5-hexenyl radicals mediated by tributyltin hydride in a key step.[1] The highly oxygenated carbocyclic products produced in this process possess considerable synthetic utility because of their application to the total synthesis of biologically important molecules such as enzyme regulators,[2a] the Corey lactone and related prostaglandin intermediates,[2b] and carbocyclic ribose derivatives.[2c,d]

A quite different solution to this synthetic problem is afforded by one-electron reducing agents and electroreductive methods which mediate a variety of carbon–carbon bond-forming processes.[3] A useful variant of this technology utilizes the reductive coupling reagent, samarium diiodide, in the intramolecular coupling of two sp^2 hybridized carbon centers in a mild and regiocontrolled ring-forming process.[4] A number of these studies involve the cyclization of aldehydes or ketones tethered to olefins which often proceed with high levels of diastereoselectivity.[5,6] We would now like to report a novel method for the stereoselective preparation of polyhydroxylated carbocycles from carbohydrate templates[7] mediated by the one-electron transfer agent, samarium diiodide. These studies also demonstrate a surprising reversal in the diastereoselectivity in the products depending on whether the olefin geometry of the starting carbohydrate is cis or trans. Finally, to our knowledge, no applications of samarium diiodide to carbohydrate templates have been studied.

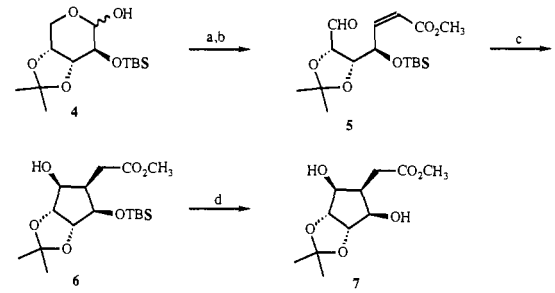
Scheme I[a]



1 2 3

[a] EWG = CO_2Me; Key: (a) $Ph_3P{=}CH{-}EWG$, H^+ (0.1 equiv), CH_2Cl_2; (b) PDC, CH_2Cl_2; (c) SmI_2, THF, MeOH, −78 °C.

Scheme II[a]



4 5 6 7

[a] Key: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, $PhCO_2H$ (0.1 equiv); (b) PDC, CH_2Cl_2, 3 Å sieves, HOAc (0.1 equiv); (c) SmI_2 (2 equiv), THF, MeOH, −78 °C; (d) nBu_4NF, THF, 0 °C.

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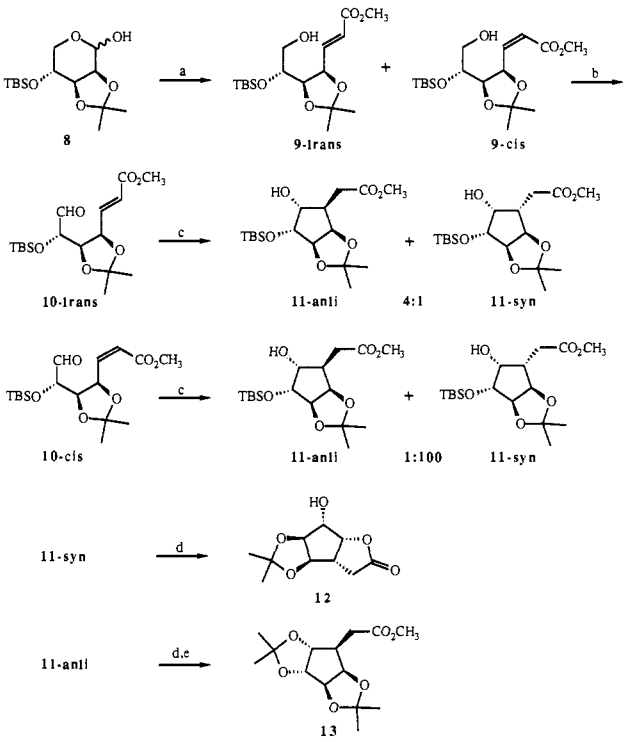
The general strategy which permits the conversion of pyranose sugars into highly oxygenated cyclopentanoid compounds is illustrated in Scheme I. Thus, protected carbohydrate lactol **1** undergoes a Wittig reaction with a stabilized ylide and subsequent pyridinium dichromate oxidation to produce substrate **2**. When treated with SmI_2, a reductive cyclization between the carbonyl and the β-carbon of the olefin then renders the desired polyhydroxylated cyclopentane compound **3**, in which a new C_1–C_5 bond (carbohydrate numbering) is formed between two sp^2 centers. In the overall sequence, the sp^3 alcohol stereocenter at C_5 is destroyed when oxidation occurs, and it is subsequently reinstated, upon treatment with SmI_2, to form a new hydroxyl bearing stereocenter. Existent 5-hexenyl free radical methods for the cyclization of carbohydrates[1] do not allow for the incorporation of this additional sp^3 alcohol center which provides further functionality for subsequent synthetic manipulations.

The aforementioned sequence was reduced to practice when lactol **4**,[8] readily available in four steps from D-(−)-arabinose by simple carbohydrate manipulations,[9] was converted to the acyclic alkene aldehyde **5** by Wittig condensation and oxidation in 74% and 73% yields, respectively, shown in Scheme II. The major *Z* geometric isomer could be easily isolated from the 10:1 *Z*:*E* olefin mixture by flash chromatography. This reversal in stereochemistry from the normally favored trans geometry from a stabilized ylide has been observed with other carbohydrate lactols.[10] Subsequent treatment with samarium diiodide[11] in the presence of methanol as a proton donor produced an almost exclusive stereochemical result (99:1 by capillary GC analysis), **6**, in 69% isolated yield. A small amount (<10%) of a dimerized carbohydrate product which was incompletely identified was also present in the reaction. The syn stereochemistry in the major product was unequivocally established by both 2-D NOESY experiments and by chemical structure transformations. In these studies, a plane of symmetry was revealed by removing the *tert*-butyldimethylsilyl protecting group, producing syn-diol **7** which possesses the stereochemistry shown via spectroscopic confirmation by a simple ^1H NMR and a 9 line ^{13}C NMR spectrum.[12] *It is particularly noteworthy that a single stereochemical result was obtained from four possible products.*

In another example of the reductive cyclization process, shown in Scheme III, the relationship of the olefin geometry in the starting substrate vs the product diastereoselectivity of the new σ-bond was examined.[6] Thus, the α,β-unsaturated esters **9**-*cis* and **9**-*trans* were obtained by a Wittig reaction as an ca. 3:1 geometric mixture from the protected D-lyxose lactol derivative **8**[13] in 59% and 21% yields, respectively.[10] After separation of the

Scheme III[a]



[a] Key: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, $PhCO_2H$ (0.1 equiv); (b) PDC, CH_2Cl_2, 3 Å sieves, HOAc (0.1 equiv); (c) SmI_2 (2 equiv), THF, MeOH, −78 °C; (d) nBu$_4$NF, THF, 0 °C; (e) 2,2-dimethoxypropane/acetone, 1:3, *p*-TsOH (catalyst).

two alcohols by flash chromatography, they were oxidized independently to afford aldehydes **10**-*cis* and **10**-*trans*, in 80% and 81% yields, respectively. When **10**-*trans* was treated with SmI_2, two polyoxygenated cyclopentane products were observed in a 4:1 ratio, **11**-*anti* and **11**-*syn*, respectively, from which the major product could be obtained in 64% yield. In marked contrast, when **10**-*cis* was treated under identical conditions, **11**-*syn* was obtained as an almost exclusive product (100:1 by capillary GC analysis) which was chromatographically isolated in 73% yield. No other products (>2%) were observed in either reaction.

The stereochemistry of **11**-*syn* was confirmed by removal of the *tert*-butyldimethylsilyl protecting group which caused simultaneous γ-lactonization to produce tricyclic alcohol **12**. A subsequent X-ray structure determination confirmed the stereochemistry as shown. The stereochemistry of **11**-*anti* was confirmed by removal of the *tert*-butyldimethylsilyl protecting group which did not cause concomitant lactonization in this case and suggested that the two new appendages were now anti. Fortunately, standard acetonide formation prepared tricyclic methyl ester **13** and demonstrated that the two alcohols were cis disposed on the cyclopentane ring. Because **11**-*anti* is indeed spectroscopically different from **11**-*syn*, this confirms that the methyl ester appendage must be β-disposed in tricycle **13**.

Perhaps the most interesting observation in these examples is the correlation of the olefin geometry in the starting substrate with the product stereochemistry. It would appear that a *cis*-olefin in the starting substrate favors a syn product and a *trans*-olefin favors an anti product. The predominance of the anti product from a *trans*-olefin has also been reported in several related noncarbohydrate cases.[6]

In summary, a stereoselective method for the preparation of highly oxygenated cyclopentane substrates has been achieved by the treatment of modified carbohydrate templates with samarium

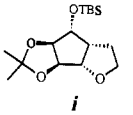
(8) All new compounds have IR, NMR, mass spectrum, combustion analysis, or accurate mass data consistant with the structure shown.

(9) Prepared from D-(−)-arabinose by the following four-step sequence: (a) benzyl alcohol, *p*-TsOH, 63%; (b) acetone, 2,2-dimethoxypropane, *p*-TsOH, 68%; (c) *tert*-butyldimethylsilyl chloride, CH_2Cl_2, Et_3N, 4-DMAP; (d) Li, NH_3, 81% for two steps.

(10) The C_5 hydroxyl functionality appears to play a role in the formation or decomposition of the ylide in the Wittig reaction. This effect was recently observed in furanose sugars, and it was strongly dependent on the type of carbohydrate examined, see: Webb, T. H.; Thomasco, L. M.; Schlachter, S. T.; Guadino, J. J.; Wilcox, C. S. *Tetrahedron Lett.* **1988**, 6823.

(11) In a general experiment, the carbohydrate (1.0 equiv) was dissolved in THF–MeOH (3:1, 1.00 M) and drawn into a syringe. Samarium diiodide (0.10 M in THF, 2.0 equiv) was cooled to −78 °C, and the solution of the carbohydrate was added dropwise over a period of 15 min. After 1 h, the reaction was generally complete by TLC analysis, and the reaction was quenched with aqueous saturated $NaHCO_3$ and extracted with ethyl acetate. Concentration and flash chromatography produced the polyoxygenated cyclopentane.

(12) Although compound **6** resisted several attempts to undergo lactonization, a cyclization to produce **i** and confirmation of the syn stereochemistry was eventually achieved by a three-step treatment with (a) LAH, THF; (b) Ph_3P, CBr_4, CH_2Cl_2; and (c) NaH, THF. For a conceptually similar proof of syn stereochemistry in bicyclo[3.3.0]ring systems, see: Kigoshi, H.; Imamura, Y.; Niwa, H.; Yamada, K. *J. Am. Chem. Soc.* **1989**, *111*, 2302.



i

(13) Prepared from D-lyxose by the following four-step sequence: (a) benzyl alcohol, *p*-TsOH, 63%; (b) acetone, 2,2-dimethoxypropane, *p*-TsOH, 68%; (c) *tert*-butyldimethylsilyl chloride, CH_2Cl_2, Et_3N, 4-DMAP; (d) Li, NH_3, 80% for two steps.

diiodide. We are currently examining other carbohydrate precursors and the accompanying stereochemical consequences of this reaction and will report these studies in due course.

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Intramolecular Photochemical Addition Reactions of ω-Styrylaminoalkanes

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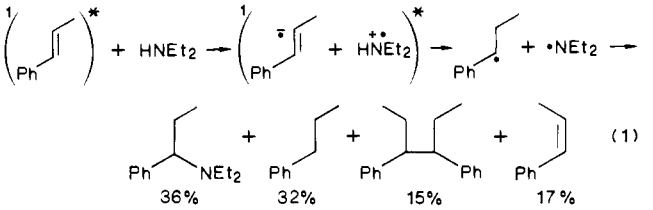
Intramolecular arene–olefin and enone–olefin photochemical cycloaddition reactions have attracted considerable interest as methods for the construction of strained polycyclic natural and unnatural products.[1] Intramolecular arene–amine and enone–amine photochemical addition reactions provide potential routes to nitrogen-containing heterocycles; however, these reactions have received relatively little attention. The intramolecular addition reactions of several secondary phenanthrylalkylamines have been reported by Sugimoto et al.,[2] and Aoyama and co-workers[3] have investigated the reactions of several tertiary styrylalkylamines, amides, and ureas. Recently Xu et al.[4] have reported the cyclization reactions of some α-silyl amine–α,β-unsaturated ketone and ester systems. To date, such reactions have been limited to the formation of five- and, less often, six-membered rings. However, since intramolecular exciplex formation has been observed for ω-aryl-α-(dimethylamino)alkanes with as few as 1 and as many as 11 methylene groups separating the chromophores,[5] it occurred to us that intramolecular arene–amine photochemical addition might provide a route to cyclized products with a wide range of ring size. We report here our preliminary results for a series of *N*-methyl-ω-(β-styryl)aminoalkanes, which serve to establish the versatility of the intramolecular styrene–amine cyclization reaction.

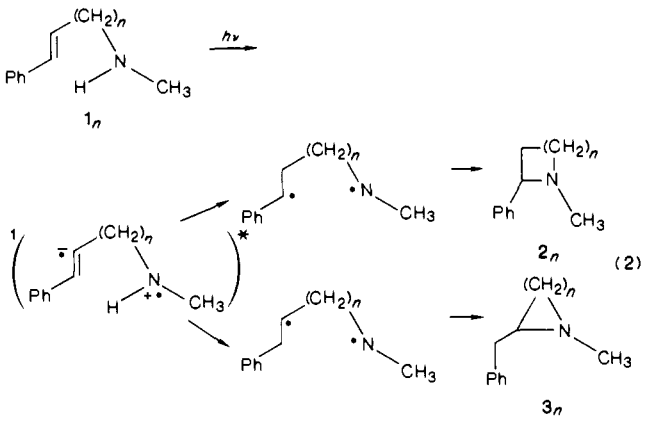
The intermolecular photochemical addition of amines to styrenes was initially reported by Cookson et al.[6] We find that the fluorescent singlet state of *trans*-1-phenylpropene (τ = 7.5 ns, Φ_f = 0.34) is quenched by diethylamine with a rate constant of 1.2 × 10^{10} M^{-1} s^{-1},[7,8] near the rate of diffusion in cyclohexane solution. Singlet quenching results in the formation of a single adduct, 1-phenylpropane, and the dimer of the 1-phenylpropyl radical (mixture of diastereomers, eq 1).[9] As was previously observed



(1)

for the reactions of singlet *trans*-stilbene and 9-cyanophenanthrene with secondary amines,[10] addition occurs in both polar and nonpolar solvents. While no exciplex fluorescence is observed, it appears likely that radical pair formation occurs via a charge-transfer-stabilized exciplex (eq 1).

The photophysical and photochemical behavior of a series of ω-(β-styryl)-α-(methylamino)alkanes ($\mathbf{1}_n$, where n = 1–5) is summarized in Table I. Singlet lifetimes and fluorescence quantum yields are all smaller than the values for 1-phenylpropene, indicative of the occurrence of intramolecular quenching of the styrene singlet by the secondary amino group. No exciplex emission is observed for secondary or primary styryl amines; however, the tertiary analogues of $\mathbf{1}_2$–$\mathbf{1}_4$ display strong exciplex fluorescence.[11] Upon irradiation in dilute solution the styryl amines undergo trans,cis isomerization and intramolecular addition to yield mixtures of α-phenyl- (**2**) and α-benzylcycloalkylamines (**3**) (eq 2).[9] The ratios of adducts **2**/**3** and total adduct/isomerization obtained at moderate conversions (<30%) in acetonitrile solution are reported in Table I. At higher conversions, adducts account for >80% of consumed starting material for $\mathbf{1}_2$–$\mathbf{1}_4$, 50% for $\mathbf{1}_5$, and 15% for $\mathbf{1}_1$. Quantum yields for total adduct (**2** + **3**) formation from $\mathbf{1}_2$, $\mathbf{1}_3$, and *cis*-$\mathbf{1}_3$ are 0.034, 0.11, and 0.19, respectively, and are lower for the other styryl amines. The total adduct yield is not strongly dependent upon solvent polarity; however, the adduct ratio is strongly solvent dependent. Values of **2**/**3** in cyclohexane solution for $\mathbf{1}_2$, $\mathbf{1}_3$, and $\mathbf{1}_4$ are reported in Table I.



(2)

By analogy to the mechanism of intermolecular styrene–amine addition (eq 1), electronic excitation of the styryl amines $\mathbf{1}_n$ is proposed to yield a locally excited singlet styrene that reacts with the amino group to form an intramolecular exciplex. The chain-length dependence of the singlet lifetime (Table I) for n = 3 < 2 < 4 < 5 reflects the tendency to form an exciplex, as

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