Synthesis of Vinyl- and Alkynylcyclopentanetetraols by SmI_2/Pd(0)-Promoted Carbohydrate Ring-Contraction

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A variety of vinyl- or alkynyl-substituted polyhydroxylated cyclopentanes and cyclobutanes are prepared in enantiomerically pure form from appropriate carbohydrate precursors, in a direct one-step ring-contraction procedure promoted by SmI_2 and catalytic Pd(0). This reaction is thought to proceed through intermediate ring-opened allyl- or allenylsamarium complexes that undergo ring-closure by intramolecular carbonyl addition. A predominant trans relationship is found between vinyl (or alkynyl) and hydroxyl groups at the two newly created stereogenic centers, with good to excellent levels of stereoselectivity being observed in the formation of homopropargyl cyclopentanol products. Under appropriate conditions, preparatively useful yields are realized of stereoisomers not directly available using alternative methodology.

Introduction

Besides their biological relevance,[1] carbohydrates are also becoming increasingly important in synthesis due inter alia to a high chirality content that can be transferred into a variety of products, leading to the construction of functionalized chiral carbocyclic and heterocyclic building blocks.[2] The transformation of carbohydrate derivatives into functionalized carbocycles has been most commonly achieved by multistep protocols involving the initial conversion of the carbohydrate into suitably functionalized open-chain products, followed by ring closure using conventional procedures.[3] Alternatively, the cyclic carbohydrate skeleton has been extensively used as a template on which to build the carbocyclic structure, using the chirality and functionalization of the carbohydrate both as stereocontrolling elements and versatile synthetic tools.[4] In contrast, the *direct* one-pot generation of a carbocyclic structure from the carbon framework of a carbohydrate derivative is much less common.[2h,5] Furthermore, in some instances, the conversion of carbohydrates into carbocycles makes use of methodology that leaves the resulting carbocycle devoid of some of the functionality present in the original carbohydrate-derived substrate. This last aspect acquires particular relevance when the products need to be further elaborated into more complex targets. Among others,[2h] methods based on the intramolecular carbonyl addition of allyl-[6,7] or propargyl-[8] metals overcome this problem, as the resulting products retain versatile and useful unsaturated groups capable of further synthetic transformations. Thus, the use of allylzirconium species generated from vinyl carbohydrate derivatives **I** has produced carbocycles **III** by intramolecular allylation, in a direct one-pot

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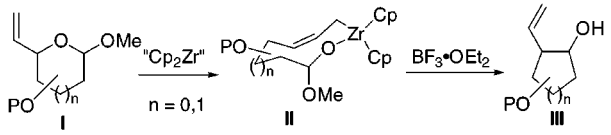
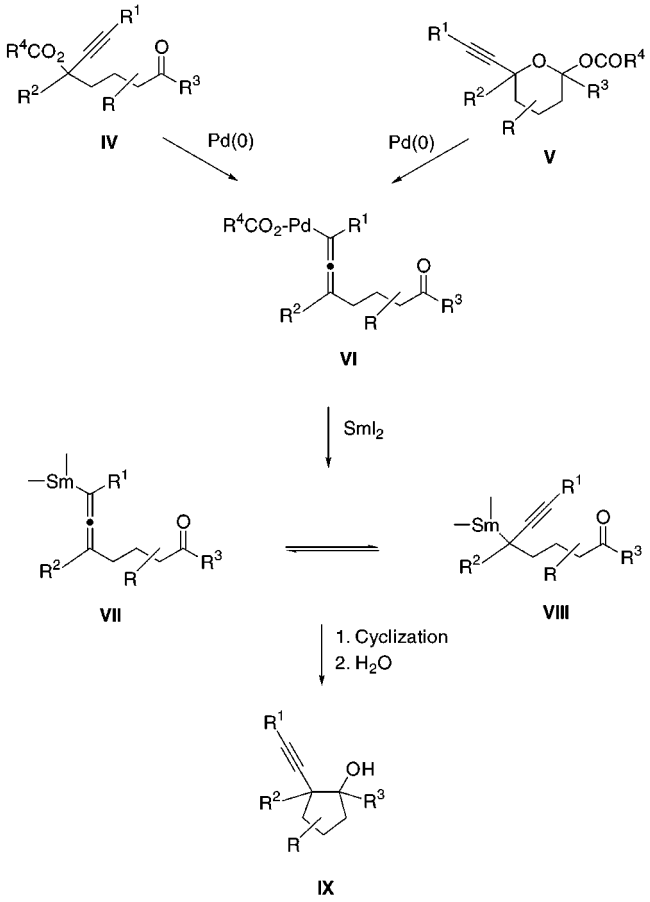
Scheme 1



carbohydrate ring-contraction (Scheme 1).[7j,7k] This procedure has proven very effective in the formation of polyhydroxylated vinyl-substituted cyclopentanes and cyclobutanes, amenable to further transformation into biologically active substances.[7j,k] However, it gave poor results when a triple bond was utilized in place of the vinyl group.[9] A general method for direct conversion of carbohydrate-like structures into vinyl- or alkynyl-functionalized enantiomerically pure carbocycles would be a useful addition to the organic chemist synthetic repertoire.

We have recently reported an efficient SmI_2/Pd(0)-promoted intramolecular propargylation of carbonyl groups using propargylic ester substrates **IV** (Scheme 2) as synthetic equivalents of the propargyl anion synthon.[8] This reaction is thought[10] to involve the initial formation of an allenylpalladium complex **VI** that is rapidly reduced by SmI_2[11] to an equilibrium mixture of allenic (**VII**) and propargylic (**VIII**) organosamarium intermediates that finally add to the carbonyl group. An important limitation of this procedure is the requirement that a tethered *ketone* carbonyl group must be employed to obtain good yields of the corresponding homopropargyl cycloalkanol products **IX**. When aldehydes are used, rapid SmI_2-promoted carbonyl reduction and/or reductive dimerization prevail over formation of **IX**. In an effort to overcome this limitation, we hypothesized that related substrates **V** derived from the corresponding propargylic lactols, when treated with SmI_2/Pd(0), could also enter the pathway **VI**-through-**VII**/**VIII** to afford the same products **IX**. It was realized that the aldehyde function, which is masked in **V**, would be released into the reaction

Scheme 2



medium simultaneously with the allenylpalladium moiety. In this way, control of the amount of free aldehyde present in the medium, exerted by the molar percentage of catalyst used, could lead to minimization of side reactions. We have successfully applied this procedure to the synthesis of certain bicyclic homopropargyl alcohols[12,13] from lactol esters **V** and now report the extension of this chemistry to the direct conversion of vinyl- and alkynylpyranosides or furanosides, derived from naturally ocurring carbohydrates, into functionalized enantiomerically pure cyclopentanes or cyclobutanes, respectively.[14]

Results

Synthesis of 6-Eno- and 6-Ynopyranosides. The substrates used in this study were synthesized from

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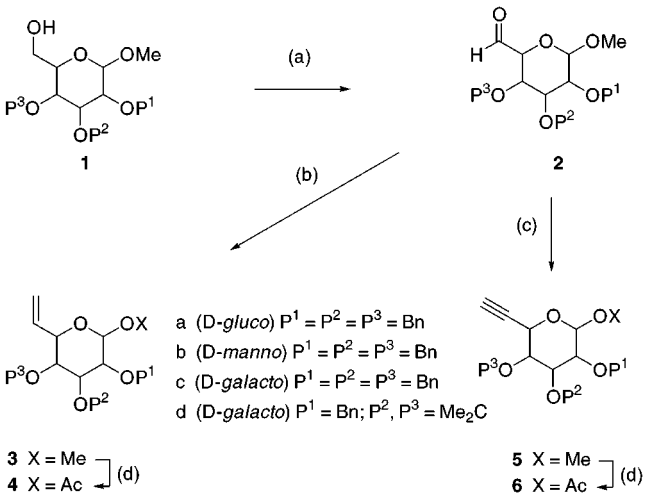
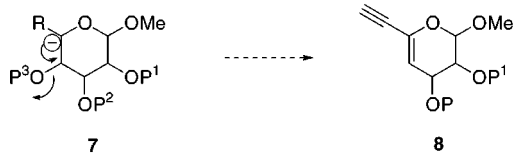
Scheme 3



(a) (i) DMSO, $(COCl)_2$, CH_2Cl_2, -40 °C; (ii) Et_3N, -40 °C to rt. (b) $Ph_3P{=}CH_2$, THF, -78 °C to rt. (c) (i) CBr_4, Ph_3P, 0 °C or CBr_4, Ph_3P, Et_3N, rt; (ii) *n*-BuLi, THF, -100 °C or LDA, THF, -78 °C. (d) Ac_2O, H_2SO_4, 0 °C.

commercially available carbohydrate derivatives as shown in Scheme 3. Thus, methyl gluco-, manno-, and galactopyranosides were transformed into alcohols **1** using conventional protection−deprotection protocols.[15] Swern oxidation of **1**, according to the procedure described by Sinaÿ,[23] afforded aldehydes **2**. After azeotropic removal of water of hydration, these were submitted to olefination or alkynylation procedures to yield vinyl- or ethynylcarbohydrate derivatives **3** or **5**, respectively, as outlined in Scheme 3. Thus, the standard Wittig olefination conditions with $Ph_3P{=}CH_2$ gave good overall yields (46−76%, two steps from **1**) of 6-enopyranosides **3**. For the synthesis of alkynes **5**, modified Corey−Fuchs[24] procedures[25−27] were applied, the best overall results being obtained with the use of $CBr_4/Ph_3P/Et_3N$ at room temperature[26] for initial dibromoolefin formation, and LDA at −78 °C[27] in the final elimination step. Slow addition of LDA and careful monitoring of the progress of the reaction were found important. This procedure avoided the presence of excess base in the reaction mixture, which otherwise led to the formation of enynes **8** by base-promoted elimination of a C4-alkoxide from an anion intermediate **7** (Scheme 4). The same problem was encountered in the attempted direct one-step alkynylation of **2d** with dimethyl 1-diazo-2-oxopropylphosphonate,[28] that yielded the corresponding enyne **8** (P^1 = Bn; P = H) in very good yield (83%), instead of the expected **5d**. The alternative use of lithium trimethylsilyldiazomethane[29] was essayed with **2a** but this did not significantly improve the yield of the Corey−Fuchs procedure, and purification of the product was more troublesome. Treatment of acetals **3** or **5** with Ac_2O/H_2SO_4[30] led to the corresponding acetates **4** or **6**, respectively (56−90% yields). These were generally obtained as diastereomeric mixtures at C1, where the α-anomer predominated.

Scheme 4



Reactions of 6-Enopyranosides with SmI_2/Pd(0). Substrates **3** and **4** were reacted under a variety of conditions with SmI_2 (3 equiv) and a catalytic amount of a Pd(0) complex (5−10 mol %) to afford in all cases the expected cyclopentanols **9** as diastereomeric mixtures (Table 1). In a control experiment, treatment of **3c** with SmI_2 alone yielded recovered starting material. In general, acetals **3** required refluxing in THF for conversion into **9**, whereas, as expected based on leaving group abilities, acetates **4** were more reactive and afforded **9** already at room temperature. In all reactions run under refluxing conditions with $Pd(Ph_3P)_4$ as catalyst (entries 1, 3, 6, 9), the major diastereoisomer of **9** had a trans relationship between substituents at the two new stereogenic centers (C1, C5) created upon cyclization, while the relative orientation of these with respect to the resident substituents was substrate dependent. Thus, the major diastereoisomer of **9a** and **9b**, derived from glucose and mannose, respectively, had a free hydroxyl group on the face of the molecule opposite to that occupied by the adjacent OBn, whereas the reverse was true for the galactose-derived **9c** and **9d**. The second most abundant product in these high-temperature reactions displayed in all cases a cis relationship between the OH and vinyl groups, while the relative orientation of OH and adjacent OBn in these isomers was always trans. In contrast, reactions run at room temperature with the same catalyst had a tendency to yield increasing amounts of cis products (entries 5, 7, 8), the exception being the reaction of acetate **4a** (entry 2) where the trans selectivity actually increased at room temperature. Surprisingly, the galactose-derived substrate **3c** (β-anomer) was found to be much more reactive than the corresponding glucose- and mannose-derived **3a,b** (α-anomers), and it could be converted into cyclopentane **9c** in very high yield already at room temperature (Table 1, entry 7). However, this also resulted in a significant decrease of diastereoselectivity, as nearly equal amounts of cis- and trans-products were obtained.

(15) Benzyl-protected methyl gluco-,[16] manno-[17] and galacto-[18] pyranosides **1a**−**c** were prepared according to the three-step procedure described in ref 19. *tert*-Butyldimethylsilylation of the primary alcohol in methyl 3, 4-*O*-isopropylidene-β-D-galactopyranoside,[20] followed by benzylation and desilylation afforded alcohol **1d**.

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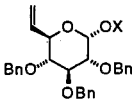
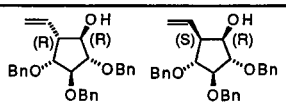
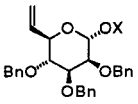
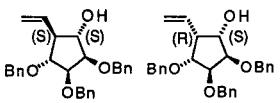
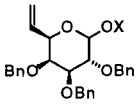
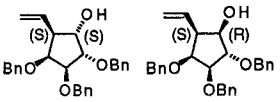
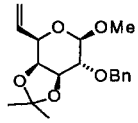
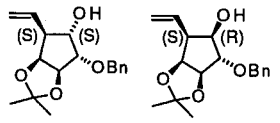
Table 1. Reactions of Vinylpyranosides 3 and 4 with SmI_2/Pd(0)[a]

Entry	Substrate	Pd(0)[b]	T (° C)	Products (9)[c]	9	Yield[d] (%)	Trans : Cis Ratio[e]
							
1	**3a** X = Me	A	75[f]	(66)	**9a**	78	69 : 31
2	**4a** X = Ac[g]	A	25	(82)	**9a**	71	82 : 18
							
3	**3b** (X = Me)	A	75[f]	(52)	**9b**	78	63 : 37
4	**3b**	C	75[f]	(37)	**9b**	51(56[h])	57 : 43
5	**4b** (X = Ac)	A	25	(17)	**9b**	70	27 : 73
							
6	**3c** (X = Me)[i]	A	75[f]	(71)	**9c**	67	74 : 26
7	**3c**	A	25	(47)	**9c**	90	54 : 46
8	**4c** (X = Ac)[j]	A	25	(47)	**9c**	98	52 : 48
							
9	**3d**	A[k]	75[f]	(70)	**9d**	79	70 : 30
10	**3d**	B	75[f]	(52)	**9d**	38(58)[h]	73 : 27
11	**3d**	C	75[f]	(55)	**9d**	50(69)[h]	68 : 32

[a] Unless otherwise indicated, 3 equiv of SmI_2 and 5 mol % of Pd(0) were used. [b] A = $Pd(Ph_3P)_4$; B = $Pd(OAc)_2 \cdot 4Bu_3P$; C = $Pd(OAc)_2 \cdot Bu_3P$. [c] Where several diastereoisomers were obtained, only structures for the two major isomers are displayed, along with their overall relative amounts within brackets. [d] Isolated total yield of **9**. Diastereomeric ratios determined by weight of isolated diastereoisomers after chromatographic separation. [e] Trans and cis refer to relative orientation of vinyl and hydroxy groups. [f] Bath temperature. [g] (α:β = 4.3:1). [h] Yield based on recovered starting material. [i] β-OMe. [j] α:β = 3.8:1. [k] A second portion of $Pd(Ph_3P)_4$ (5 mol %) was added after 2 h (total reaction time 15 h).

In reactions of allylic acetates, the use of equimolar amounts of $Pd(OAc)_2$ and *n*-Bu_3P, $Pd(OAc)_2 \cdot Bu_3P$, as an in situ source of Pd(0), has been shown to give improved results in terms of yield and diastereoselectivity.[31−34] However, in the two cases where we have applied this catalyst system, there was in fact a drop in stereoselectivity, and starting materials were partially recovered (Table 1, entries 4 and 11). Alternatively, the use of a 1:4 ratio of $Pd(OAc)_2$ to *n*-Bu_3P, $Pd(OAc)_2 \cdot 4Bu_3P$, which proved beneficial with **5** and **6** (vide infra), led to a further drop in reactivity, as **3b** was recovered unchanged, whereas **4a** and **4b** underwent extensive decomposition, and only **3d** afforded the desired product, albeit in low yield and with poor stereoselectivity (Table 1, entry 10).

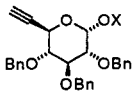
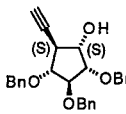
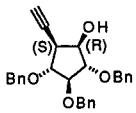
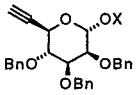
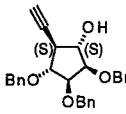
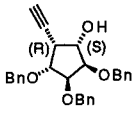
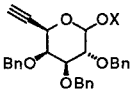
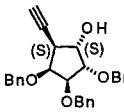
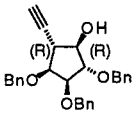
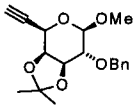
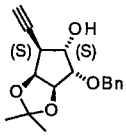
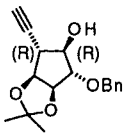
Reactions of 6-Ynopyranosides with SmI_2/Pd(0). The corresponding use of the alkynyl derivatives **5** and **6** resulted in the obtention of homopropargyl cyclopentanols **10**. Reaction conditions, yields, and diastereomeric ratios are collected in Table 2. These reactions displayed some significantly different features with respect to their vinylic counterparts. Thus, under appropriate conditions, the use of pyranosyl acetates in place of methyl pyranosides led invariably to higher yields and diastereoselectivities.[35] Also beneficial was the incorporation of *n*-Bu_3P as Pd ligand (entries 3, 7, 12). Moreover, the levels of trans selectivity (ethynyl and OH groups) were much higher in these series, to the exclusion of cis products in some cases.

In common with the vinyl series, diastereoselectivity was again substrate-dependent. Thus, while the mannose-derived cyclopentanol **10b** was formed preferentially with the same trans configuration (1*S*,5*S*) as the corresponding major vinylic product **9b**, *opposite* trans configurations were obtained for the major vinyl- (**9a**, 1*R*,5*R*) and alkynyl- (**10a**, 1*S*,5*S*) diastereoisomers in the gluco-series, and the galacto-derivatives displayed a mixed behavior that was dependent on both the peripheral protecting groups and the ligands used in the Pd catalyst. Thus, the reactions of the benzyl-protected substrates **5c** and **6c** with SmI_2 and $Pd(Ph_3P)_4$ afforded preferentially the **10c** diastereoisomer with (1*R*, 5*R*) configuration, which is opposite to that obtained from the corresponding vinyl derivatives, whereas the use of $Pd(OAc)_2 \cdot 4Bu_3P$ led predominantly to the (1*S*, 5*S*)-isomer. This was the

(31) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326−1327.
(32) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 6090−6092.
(33) Mandai, T.; Matsumoto, T.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 2513−2516.
(34) Oppolzer, W.; Flachsmann, F. *Tetrahedron Lett.* **1998**, *39*, 5019−5022.

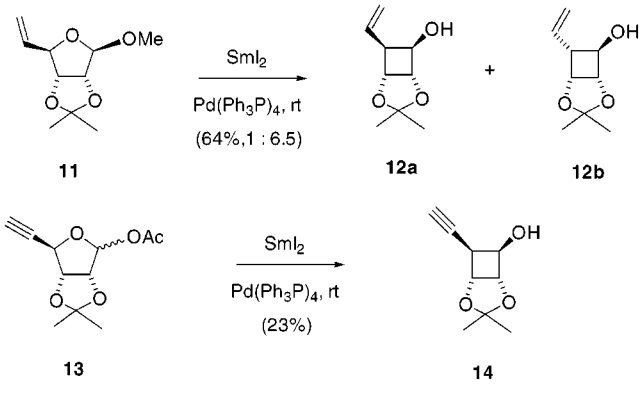
(35) However, acetates **6** underwent slow degradation when reacted at temperatures that presumably did not lead to efficient oxidative additions. See, for example, entries 6 and 7 in Table 2.

Table 2. Reactions of Alkynylpyranosides 5 and 6 with SmI_2/Pd(0)[a]

Entry	Substrate	Pd(0)[b]	T (° C)	Products (10)[c]		10	Yield[d] (%)	Trans : Cis Ratio[e]
								
1	**5a** X = Me	A	75[f]	(64)	(12)	**10a**	49[g]	≥ 71 : 29[h]
2	**6a** X = Ac	A	40	(70)	(21)	**10a**	34	≥ 70 : 30[i]
3	**6a**	B	40	(89)	(11)	**10a**	77	89 : 11
								
4	**5b** (X = Me)	A	75[f]	(72)	(28)	**10b**	75	72 : 28
5	**6b** (X = Ac)	A	25	(100)	-	**10b**	7[j]	Only *trans*
6	**6b**	B	25	-	-	-	k	-
7	**6b**	B	75	(100)	-	**10b**	82	Only *trans*
								
8	**5c** (X = Me)[l]	A	75[f]	(22)	(60)	**10c**	65	82 : 18
9	**6c** (X = Ac)[m]	A	25	(12)	(81)	**10c**	76	93 : 7
10	**6c**	B	75	(66)	(34)	**10c**	65	Only *trans*
								
11	**5d**	A	75[f]	(95)	(5)	**10d**	19	Only *trans*
12	**5d**	B	75[f]	(100)	-	**10d**	70	Only *trans*

[a] Unless otherwise indicated, 3 equiv of SmI_2 and 5 mol % of Pd(0) were used. [b] A = $Pd(Ph_3P)_4$; B = $Pd(OAc)_2 \cdot 4Bu_3P$. [c] Where several diastereoisomers were obtained, only structures for the two major isomers are displayed, along with their overall relative amounts within brackets. [d] Isolated total yield of **10**. Diastereomeric ratios determined by weight of isolated diastereoisomers after chromatographic separation. [e] Trans and cis refer to relative orientation of ethynyl and hydroxy groups. [f] Bath temperature. [g] Also obtained was cyclobutanol **18** (7%) (see Scheme 6). [h] The two isomers of undetermined stereochemistry were isolated in relative amounts of 17% and 7%. [i] One other isomer (stereochemistry not determined) was isolated in 9% relative amount. [j] Also isolated were lactol **5b**-OH (X = H) (30%), benzyl alcohol (29%), and benzyl acetate. [k] Substrate degradation. [l] β-OMe. [m] α:β = 71:29.

Scheme 5



almost exclusive configuration obtained for acetonide **10d** with both catalyst systems.

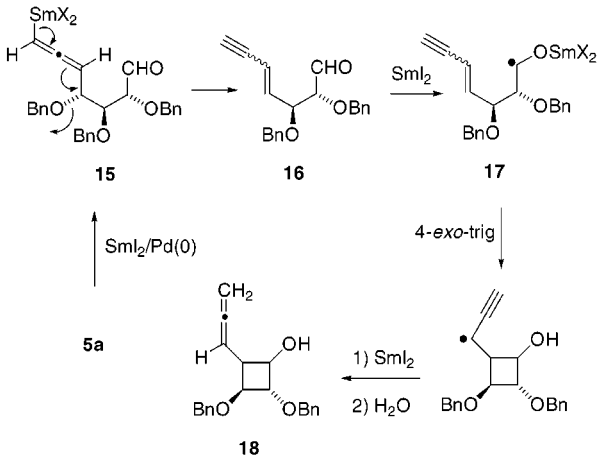
Reactions with Furanose Derivatives. The corresponding transformations using furanose substrates were also investigated (Scheme 5). The ring-contraction procedure using SmI_2/Pd(0) led to the formation of cyclobutane products, but the reaction does not appear to be of general application. Thus, vinylacetonide **11**[36] afforded at room temperature the homoallylic cyclobutanol **12** with moderate yield and trans-stereoselectivity at the vinyl- and hydroxy-bearing stereogenic centers. However, analogous Bn-protected substrates only reacted under refluxing conditions, and this led to substrate degradation and formation of benzyl alcohol as the only identifiable product. The reaction of the propargylic substrate **13** at room temperature led to a low yield of the corresponding homopropargyl alcohol **14**.

Stereochemical Elucidation. In most cases the diastereoisomers were readily separated by liquid chromatography. Vinylcyclopentanols (1*R*,5*S*)-**9a**, (1*S*,5*R*)-**9b**, and (1*S*,5*R*)-**9c** were characterized by direct comparison of their ^1H and ^{13}C NMR spectra with data previously reported in the literature for the same compounds.[37] The stereochemical elucidation of the rest of isolated cycloalkanol products was made unambiguously with the aid of NOE effects. As a general rule, for pairs of protons on adjacent ring carbons, a percent NOE ≥ 9 was taken as

(36) Ryan, K. J.; Arzoumanian, H.; Acton, E. M.; Goodman, L. *J. Am. Chem. Soc.* **1964**, *86*, 2503−2508. Prepared by Wittig olefination with $Ph_3P{=}CH_2$ of the corresponding aldehyde precursor, itself prepared according to: Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853−3857.

(37) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835−8836.

Scheme 6



an indication of a cis relationship between those protons, whereas values of NOE ≤ 5 led normally to a trans assignment. For pairs of protons on nonadjacent ring carbons, the observation of NOE effects was interpreted as indicative of cis relationships. All observed effects were consistent with the assigned structures. A chart with the most significant NOE data is included with the Supporting Information.

Discussion

The SmI_2/Pd(0)-mediated direct conversion of 6-eno- and 6-ynopyranosides into functionalized carbocycles is a practical procedure for the preparation of enantiomerically pure functionalized carbocyclic building blocks. Substrates are simply made in a few steps, with reliable reactions, and the major carbocyclic products are in most cases readily separated by liquid chromatography in preparatively useful yields. For a given configuration of the starting carbohydrate, different stereochemical outcomes are possible depending mainly on (i) type of substrate (allylic or propargylic); (ii) reaction conditions; and (iii) palladium ligands. As a consequence, the method gives ready access to stereoisomers which are not directly available using alternative methodology.

The formation of cycloalkanol products is readily rationalized as the result of a Pd(0)-promoted ring-opening of **3**−**6**, **11**, **13**, followed by reduction of an intermediate π-allyl- or allenylpalladium complex (see, for example, **VI** in Scheme 2 for allenyl case), and carbonyl addition of the resulting organosamarium (eg **VII**, **VIII**). The initial oxidative addition leading to **VI** may be facilitated by coordination of the endocyclic or exocyclic acetal-type oxygens of **V** to Lewis-acidic Sm(III) species, formed in the reduction step, or to SmI_2 itself.[38] Additionally, in six-membered cyclic substrates, both axial and equatorial orientations of the exocyclic leaving group are tolerated. While a higher degree of concertedness is possible when the leaving group is equatorial (e.g., **3c**, **3d**, **5c**, **5d**), stereoelectronic assistance provided by the endocyclic oxygen to an axially oriented leaving group may also be beneficial, providing oxocarbenium-like character during ring-opening. Interestingly, out of all of the acetal derivatives **3** or **5**, the vinylic **3c**, with an equatorial OMe, was the only one capable of reaction at room temperature (Table 1, entry 7). The reason for this enhanced reactivity resides likely in the less-hindered S_N2' approach of the palladium catalyst when the C4 substituent is axial, rather than in an inherently higher reactivity of the equatorially disposed leaving group.[39] This effect was not observed in the corresponding propargylic substrate **5c**, which is expected to be intrinsically less reactive.[40]

Always latent in these reactions is the possibility of unwanted elimination of a samarium alkoxide[41] between the organosamarium moiety and an adjacent alkoxy substituent in intermediates analogous to **VII**, **VIII** (Scheme 2). Indeed, a small amount (7%) of the allenyl cyclobutanol **18** was isolated from the reaction of acetal **5a**. This product may have formed by SmI_2/Pd(0)-mediated ring-opening and reduction, followed by elimination and SmI_2-promoted 4-*exo*-trig intramolecular addition[42] of an enyne samarium ketyl radical **17**. Remarkably, out of all of the cyclopentane-forming reactions tested, this was the only instance that such a kind of product was observed. It is therefore concluded that, if organosamariums analogous to **15** are indeed intermediates in these reactions, their cyclization is faster than the alternative competing elimination.

The reactions reported here are related to the "Cp_2Zr"/BF_3-promoted ring contraction of 6-enopyranosides[37] that affords the same vinylcyclopentanols through the intermediacy of allylzirconium species **II** (Scheme 1). However, the corresponding reactions with 6-ynopyranosides have not been reported, and attempts to carry out an analogous transformation on non-carbohydrate substrates gave poor results.[9] Alternatively, the synthesis of simple alkynylcyclopentanols has been possible using allenyltitanium intermediates in a related ring-contraction method.[9] Comparison of our reactions with these precedents shows remarkable differences in stereochemical trends. Thus, while the SmI_2/Pd(0) reaction gives a high incidence of trans products, the "Cp_2Zr"/BF_3-promoted ring contraction of 6-enopyranosides affords the corresponding *cis*-vinylcyclopentanols, and the titanation of related non-carbohydrate alkynyl substrates with Ti(O*i*-Pr)$_4$/*i*-PrMgCl also leads to cis products predominantly. Therefore, this SmI_2/Pd(0)-promoted reaction and the existing methods are stereochemically complementary. Also worthy of note, with the exception of **9a**, the cis isomers obtained from substrates **3** using the "Cp_2Zr"/BF_3 method[37] are *not* the same as those afforded by the SmI_2/Pd(0) reaction.

For ring-closure reactions that proceed through allyl-[6,7f,37] or allenyl-propargyl organometallic intermediates,[43]

(38) Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023−9042.

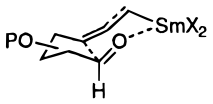
(39) Another factor that could play a role here is the electronic interaction between the axially oriented C4 substituent in **3c** and the axial lone pair of ring oxygen. This has been shown to lead to higher rates in the acid hydrolysis of certain galactopyranosides when compared with the corresponding gluco-analogues. However, it should be pointed out that these data apply to α-*anomers* that react with substantial development of oxocarbenium-like character. See MiljKovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.

(40) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589−2612.

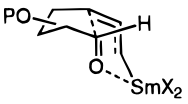
(41) Previous examples of elimination of samarium alkoxides from allenyl-propargyl intermediates: (a) Okamura, W. H.; Aurrecoechea, J. M.; Gibbs, R. A.; Norman, A. W. *J. Org. Chem.* **1989**, *54*, 4072−4083. (b) Aurrecoechea, J. M.; Solay-Ispizua, M. *Heterocycles* **1994**, *37*, 223−226. (c) Marco-Contelles, J.; Destabel, C.; Chiara, J. L. *Tetrahedron-Asymmetry* **1996**, *7*, 105−108.

(42) The SmI_2-promoted intramolecular 4-*exo*-trig addition of ketyl radicals has been described: Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913−4916.

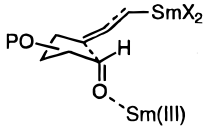
the formation of cis products is usually interpreted in terms of chelated "cyclic" transition states, whereas the corresponding "open" transition states would lead to trans products. High Lewis acidities of the organometallic species involved in C−C bond formation favor the former whereas weakly acidic organometallics and the presence of strong external Lewis acids facilitate attainment of the latter. In a close precedent, the intramolecular addition of an oxyallylsamarium, generated from a vinyloxirane, to an appended ketone at −30 °C affords a cyclized product with cis stereochemistry, presumably through a chelated transition state.[7p] Thus, in our case, the observed stereochemical trends could be interpreted as the result of competing chelated (**X**, **XI**) and nonchelated (**XII**, **XIII**) transition structures originated from intermediate



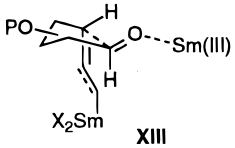
X



XI



XII



XIII

allylic or propargylic organosamariums in the ring-closure step. In light of the foregoing precedent, the high incidence of trans products observed in the SmI_2-promoted ring-contractions may be surprising. Thus, the formation of cis products through chelates **X**, **XI** is expected to be favored by the known high oxophilicity associated to Sm(III) species. However, the alternative **XII**, **XIII**, that leads to the corresponding trans products, is similarly favored by coordination of the carbonyl group to bulky solvated Sm(III) resulting from SmI_2-promoted reductions. Incidentally, these SmX_3 species are expected to be more Lewis acidic than the nucleophilic organosamariums ($RSmX_2$) directly involved in bond formation. In this scenario, chelated structures would be more easily attained from allylsamariums than from the linear allenic-propargylic species, thus leading to the higher trans selectivity observed for the latter. Also consistent with this reasoning, in the allylic series, the formation of trans products is observed to be favored by high temperatures,[44] that probably cause the rupture of the samarium chelate. Conversely, the reported[7p] cyclization of an oxyallylsamarium at −30 °C leads, as mentioned above, to the exclusive formation of a cis product.

More difficult to explain is the relationship between the configuration of C1, C5 and that of their respective adjacent stereogenic centers in the formation of cyclopentanols **9** and **10**. This is found to be dependent on (i) configuration and structural features of starting carbohydrate, (ii) type of substrate (allylic or propargylic), and (iii) palladium ligands. For vinylcyclopentanols **9**, the stereocontrolling element appears to be the tendency of the free hydroxyl group to be oriented trans (probably for steric reasons) to the adjacent alkoxy substituent.[45] However, the opposite trend is frequently observed in the formation of alkynylcyclopentanols **10** and, in one case, the tendency is reversed with a change in Pd ligands.[46] Clearly, the mechanistic aspects of these SmI_2/Pd(0)-promoted reactions appear to be somewhat more complex than the simple picture just outlined, and a convincing explanation for these observations cannot be given at this point. Additional factors that would need to be considered may include (i) the configuration and configurational stability of the organometallic species involved in cyclization[48] and (ii) the stereoelectronic impact[6] of substituents upon the stereochemistry of cyclization. Particularly intriguing is the close similarity between the stereochemical trends observed for reactions of vinyl substrates **3** and those reported for SmI_2-promoted *radical* cyclizations of carbohydrate-derived ω-unsaturated aldehydes.[49] To address these points, it would be helpful to study simpler substrates to isolate the effect of each individual substituent. At the same time, further changes in the catalyst ligands and in the nature (e.g., Lewis acidity) of the metal involved in cyclization might help to better define the characteristics of the cyclization step. Efforts toward these goals are under way and will be reported in due course.

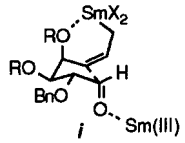
Conclusion

The SmI_2/Pd(0)-promoted carbohydrate ring-contraction provides easy access to a variety of stereochemically defined enantiomerically pure carbocycles while preserv-

(43) Kadota, I.; Hatakeyama, D.; Seki, K.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 3059−3062.

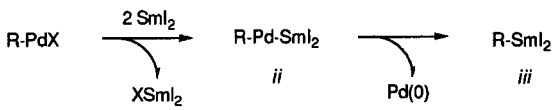
(44) Examples of chelate-related, temperature-dependent stereoselectivity abound in SmI_2 chemistry. See, for example: (a) Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447−7448. (b) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373−376. (c) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *J. Org. Chem.* **1997**, *62*, 8902−8906. (d) Matsuda, F.; Kawatsura, M.; Hosaka, K.; Shirahama, H. *Chem. Eur. J.* **1999**, *5*, 3252−3259.

(45) The exception is the formation of **9c** and **9d**, where the formation of the major isomer under refluxing conditions could be explained by the intermediacy of the chelate *i*.



i

(46) The use of *n*-Bu_3P ligands in place of Ph_3P was initially prompted by the apparent need for a more reactive Pd(0) in reactions of acetates **6a** and **6b**, that were sluggish with $Pd(Ph_3P)_4$ (Table 2, compare entries 2 and 5 with 3 and 7, respectively). The additional observation of changes in diastereoselectivity with changes in the Pd(0) ligands is interesting. It could be interpreted as an indication that phosphane ligands are incorporated in the coordination sphere of the Sm(III) species involved in cyclization. Alternatively, it has been recently suggested[47] that the SmI_2/Pd(0)-promoted *in situ* generation of allylsamarium intermediates may proceed through an oxidative transmetalation pathway that would presumably involve bimetallic species *ii* (R = allyl). If *ii* rather than *iii* were also the nucleophilic species involved in cyclization, changes in the palladium ligands could bring about diastereoselectivity differences through changes in the Lewis acidity and the electron-donating ability of the metallic moiety.



(47) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214−8219.

(48) For example, the Pd(0)-mediated oxidative addition of propargylic esters is kwown to take place with inversion of configuration and the resulting allenylpalladium complexes appear to be configurationally stable. However, no data are available on the preferred stereochemical pathway of the ensuing reductive transmetalation to Sm. In any case, the diastereoisomer distribution in most SmI_2/Pd(0) ring-contraction reactions indicates that, at least to some extent, stereochemical scrambling takes place, probably at the organosamarium level.

ing useful and versatile functionality in the final products. These features will enable their use as functionalized building blocks suitable for further elaboration into more complex targets. A trans relationship between the two newly created stereogenic centers is observed in many cases and this nicely complements related existing methodology for direct carbohydrate to carbocycle conversion. In most cases, an appropriate choice of substrate structural features and reaction conditions allows the selective preparation of one stereoisomer out of four possible, in preparatively useful yields.

Experimental Section

General. All reactions involving air- and moisture-sensitive materials were performed using standard benchtop techniques.[53] Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone and, for reactions with SmI_2, it was deoxygenated prior to use. Acetic anhydride, CH_2Cl_2, DMSO, DMF, pyridine, triethylamine, and diisopropylamine were distilled from CaH_2. EtOH and MeOH were dried by treatment with $Mg-I_2$ and distillation. Carbon tetrabromide was purified by sublimation. Triphenylphosphane was purified by recrystallization from hexanes. *n*-Tributylphosphane (Fluka, 95%) was used from a Sure-Seal bottle. Flash column chromatography[54] was performed on silica gel (230−400 mesh). HPLC purifications were carried out with a LiChrosorb Si60 column (7 μm, 25 × 2.5 cm) using a refraction index detector. Routine ^1H and ^{13}C NMR spectra were obtained at 250 and 62.9 MHz, respectively, using $CDCl_3$ as solvent and internal reference (δ 7.26 for ^1H and δ 77.0 for ^{13}C). IR data include only characteristic absorptions. Mass spectra were obtained at 70 eV.

General Procedures for Oxidation of Alcohols 1 and Wittig Methylenation. Preparation of Enopyranosides 3. In a typical experiment, to a solution of oxalyl chloride (760 μL, 8.7 mmol) in CH_2Cl_2 (35 mL) at −40 °C under argon was added dimethyl sulfoxide (710 μL, 10.0 mmol). After 10 min a solution of **1** (6.7 mmol) in CH_2Cl_2 (12 mL) was added, and the resulting mixture was stirred for 1 h at −40 °C. Triethylamine (2.8 mL, 20.1 mmol) was then added, and the mixture was allowed to reach rt over a period of 30 min. The solution was successively extracted with saturated $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue that was dissolved in benzene and evaporated (three times) to yield the intermediate aldehyde **2**. Without further manipulation, this crude aldehyde was used in the next step as follows. *n*-BuLi (1.4 M in hexanes, 5.5 mL, 7.7 mmol) was added to a suspension of methyltriphenylphosphonium bromide (2.80 g, 7.84 mmol) in THF (28 mL) at 0 °C. After 30 min the mixture was cooled at −78 °C, and a solution of the foregoing aldehyde in THF (9 mL) was added. After 15 min, the reaction mixture was allowed to warm to room temperature, and saturated NH_4Cl (20 mL) was added. The aqueous phase was extracted with Et_2O, and the combined organic extracts were dried (Na_2SO_4). The crude after evaporation was purified by flash chromatography to yield alkenes **3**. Purification and characterization data are given in the Supporting Information.

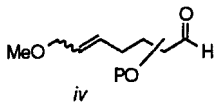
General Procedures for Dibromomethylenation of Aldehydes 2. Method A: In a typical experiment, to a solution of CBr_4 (4.87 g, 14.7 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added dropwise a solution of Ph_3P (7.74 g, 29.5 mmol) in CH_2Cl_2 (20 mL). The resulting slurry was allowed to reach rt and was stirred further 20 min. The mixture was cooled to 0 °C, and a solution of the appropriate aldehyde **2** (6.85 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was allowed to reach rt and, after 20 min, the resulting slurry was filtered trough a SiO_2 path (2 cm, $\phi = 4.2$ cm). The solid residue was washed with CH_2Cl_2, and the residue after evaporation of the solvent was purified by flash chromatography as indicated in the Supporting Information for the individual cases. Method B: In a typical experiment, to a solution of Ph_3P (1.50 g, 5.74 mmol) in CH_2Cl_2 (4 mL) at room temperature was added dropwise a solution of CBr_4 (0.95 g, 2.87 mmol) in CH_2Cl_2 (3 mL). The resulting orange slurry was stirred 40 min at the same temperature, and then Et_3N (0.92 mL, 6.60 mmol) was added. After cooling the resulting purple slurry to 0 °C, the appropriate aldehyde **2** (1.43 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was allowed to reach rt and was stirred at that temperature for 2 h. The solvents were partially evaporated until 3−5 mL remained, and the resulting residue was filtered through a SiO_2 path (2 cm, $\phi = 4.5$ cm, saturated with Et_3N). The solid residue was washed with the minimum volume of CH_2Cl_2 and then with 25% EtOAc/hexanes. The resulting slurry was filtered, and the solvents were evaporated at reduced pressure. The crude product was purified by flash chromatography as indicated in the Supporting Information for the individual cases.

General Procedures for Dehydrobromination of Dibromoolefins. Preparation of Alkynes 5. Method A: In a typical experiment, *n*-BuLi (1.6 M in hexanes, 11.68 mmol) was added dropwise to a solution of the appropriate dibromoolefin (5.17 mmol) in THF (9 mL) at −100 °C. The mixture was kept at −80 °C for 10 min, it was then allowed to reach 0 °C, and H_2O (10 mL) was added. The layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic extracts were dried (Na_2SO_4). The crude product was purified by flash chromatography as indicated in the Supporting Information for the individual cases. Method B: In a typical experiment, a solution of LDA (0.43 M in THF, 17.6 mmol) was added dropwise to a solution of the appropriate dibromoolefin (8.0 mmol) in THF (35 mL) at −78 °C. Aditional portions of LDA (0.43 M, 2 × 4.3 mmol) were added until disappearance of the dibromoolefin as judged by TLC. After addition of H_2O (90 mL), the mixture was allowed to reach rt. The layers were separated, the aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine and then dried (Na_2SO_4). The residue obtained after evaporation of the solvents was purified by flash chromatography as indicated in the Supporting Information for the individual cases.

General Procedure for Acetolysis of Methyl Pyranosides 3 and 5. Preparation of Acetates 4 and 6. In a typical experiment, to a solution of **3** or **5** (0.54 mmol) in Ac_2O (2.87 mL, 30.4 mmol) at 0 °C was added concd H_2SO_4 (26 μL, 0.49 mmol). After 8 min, the solution was poured over H_2O (15 mL), and solid $NaHCO_3$ was added until neutral pH. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4). The residue after evaporation was purified by flash chromatography as specified in the Supporting Information for the individual cases.

Reactions with SmI_2/Pd(0). Preparation of Pd(0) catalyst solutions: $Pd(Ph_3P)_4$ (catalyst A) was prepared using the literature procedure[55] and directly dissolved in admixture with the substrate. A THF solution of $Pd(OAc)_2 \cdot 4Bu_3P$ (catalyst B)

(49) Chiara, J. L.; Martinez, S.; Bernabe, M. *J. Org. Chem.* **1996**, *61*, 6488−6489. Intramolecular radical addition of samarium ketyls to a C=C bond would be expected to afford trans products.[50] One possibility to enter a radical cyclization pathway would be the Pd(0)-mediated isomerization of allylic substrates[51] **3** to generate ring-opened intermediates *iv* capable of ketyl radical cyclization. However, attempts to effect the isomerization of **3a** or **3c** to *iv* with $Pd(Ph_3P)_4$ under refluxing conditions were unsuccessful, even in the presence of Lewis acids.[52]



iv

(50) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York,1996.

(51) Amatore, C.; Jutand, A.; Meyer, G.; Mottier, L. *Chem. Eur. J.* **1999**, *5*, 466−473.

(52) Pérez, E., Aurrecoechea, J. M. Unpublished results.

(53) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis Via Boranes*; Wiley & Sons: New York, 1975.

(54) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

was prepared by adding *n*-Bu_3P (80 μL, 0.30 mmol) to a solution of $Pd(OAc)_2$ (15 mg, 0.07 mmol) in THF (4 mL). An immediate color change from orange to yellow was observed. A portion of this solution was immediately added to a solution of the carbohydrate substrate in THF to obtain a final molar ratio of substrate to catalyst of about 19:1. A THF solution of $Pd(OAc)_2 \cdot Bu_3P$ (catalyst C) was similarly prepared using *n*-Bu_3P (37 μL, 0.14 mmol) and $Pd(OAc)_2$ (31 mg, 0.14 mmol) in THF (5 mL) and proceeding as indicated above for catalyst B. **General Ring-Contraction Procedure with SmI_2/-Pd(0)**. A SmI_2 (ca. 0.1 M in THF) was prepared as reported[11b] from Sm metal and diiodomethane. In a typical experiment, to a solution of SmI_2 (1.88 mmol) in THF (19 mL) was added a mixture of the starting carbohydrate **3**−**6** or **11** or **13** (0.63 mmol) and the Pd(0) catalyst (0.03 mmol) in THF (4 mL). The resulting solution was stirred at the temperature indicated in Tables 1, 2 and Scheme 5 until consumption of the starting material as judged by TLC (0.5−60 h). After cooling, saturated K_2CO_3 (15 mL) was added. The layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue after evaporation was purified as specified in the Supporting Information for the individual cases to afford **9**, **10**, **12**, **14**. Yields and specific reaction conditions are given in Tables 1, 2 and Scheme 5. Characterization data is included in the Supporting Information.

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Supporting Information Available: Characterization data for all new compounds and experimental procedures for **1d**, **13**; copies of ^{1}H NMR spectra for **4b**, **5d**, **6a**, (1*S*,5*R*)-**9a**, (1*R*,5*R*)-**9b**, (1*R*,5*S*)-**9c**, (1*R*,5*R*)-**9c**, (1*S*,5*R*)-**9d**, (1*R*,5*R*)-**9d**, (1*R*,5*S*)-**10a**, **10a′**, **18**, (1*S*,5*S*)-**10b**, (1*S*,5*R*)-**10b**, (1*S*,5*S*)-**10c**, (1*R*,5*R*)-**10c**, (1*S*,5*R*)-**10c**, (1*R*,5*R*)-**10d**, **12**, **14**, and chart with a summary of NOE data. This material is available free of charge via the Internet at http://pubs.acs.org.

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