Selective Deoxygenation of Unsaturated Carbohydrates with $Pd(0)/Ph_2SiH_2/ZnCl_2$. Total Synthesis of (+)-(*S*,*S*)-(6-Methyltetrahydropyran-2-yl)acetic Acid

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Highly chemoselective reductive cleavage of allylic acetates of 1,2- and 2,3-unsaturated monosaccharides was achieved by a three-component reducing system comprised of diphenylsilane, a soluble palladium(0) catalyst, and catalytic amounts of zinc chloride. It was demonstrated that hydride substitution proceeds with absolute inversion of configuration at the carbon, implying that hydride is initially transferred to palladium and from there to the allylic ligand. The usefulness of the new chiral building blocks thus formed was demonstrated by the total synthesis of the civet constituent, (+)-(2*S*,6*S*)-*cis*-(6-methyltetrahydropyran-2-yl)acetic acid and its 2*R*,6*S*-trans isomer.

Introduction

A convenient, widely applied approach to the total synthesis of optically active biochemicals and pharmaceuticals takes advantage of readily available chiral starting materials (chirons).[1] Monosaccharides are one of the most attractive sources for many such chirons. However, since most natural carbohydrates are heavily substituted by oxygen functionalities, the conversion of a given monosaccharide into a useful chiron often requires reductive cleavage of one or more of these oxygen substituents.

Several procedures have been developed for this, one of which involves transformation of the selected oxygen function into a reactive leaving group which can be substituted by a powerful hydride nucleophile[2] or homolytically cleaved at the C–O bond and the resultant alkyl radical reacted with an H-donor.[3] In addition, a carbohydrate hydroxyl group may be replaced by a halide function, followed by reductive dehalogenation.[4] A third approach involves introducing unsaturation in proximity to the oxygen function, forming an allylic leaving group[5] (e.g., producing a glycal derivative), which may be substituted by hydride under either acidic[6] or basic conditions.[7] These reactions,[8] however, usually require either strong nucleophiles or strong Lewis acids (such as $BF_3{\cdot}OEt_2$ and $SnCl_4$) or activation of the leaving group.[9,10]

activation of the unsaturated carbohydrate derivative via complexation to transition metals would be an attractive alternative to the above-described approaches, as it is expected to occur under neutral, milder conditions with a high degree of regio- and stereocontrol.

In this paper we report on a useful application of our previously described three-component reducing system[11] comprised of diphenylsilane, palladium catalyst, and zinc chloride cocatalyst for highly chemoselective reductive cleavage of allylic oxygen functions of unsaturated monosaccharides. The usefulness of the new chiral building blocks thus formed is demonstrated by the total synthesis of the civet constituent (+)-(2*S*,6*S*)-*cis*-(6-methyltetrahydropyran-2-yl)acetic acid as well as its (+)-2*R*,6*S*-trans isomer.

Results and Discussion

Glycal Derivatives. Most reports on palladium-catalyzed nucleophilic substitutions of glycal derivatives invoke (η^2-alkene)palladium(II) chemistry. For example, Pd(II)-assisted coupling of various aryl groups to the anomeric position of glycals involves carbopalladation of the double bond at position 1,2,[12] followed by either deoxypalladation or dehydropalladation.[13]

In contrast, quite limited success was encountered with respect to Pd(0)-catalyzed allylic substitution of glycal derivatives, probably due to difficulties of forming a π-allylpalladium complex with positions 1, 2, and 3 of the sugar molecule. Such complexes are formed very sluggishly when the allylic system bears an electron-donating function, such as an alkoxide group.[14] Here more forcing conditions[14,15] or better leaving groups, such as trifluoroacetate,[16] are required.

Therefore, it was not surprising that our previously reported conditions for reductive cleavage of standard allylic acetates,[17] employing palladium(0) and diphenylsilane, were totally ineffective with tri-*O*-acetylglucal **1**. However, slow reduction of **1** to **2** was observed in the presence of an appropriate Lewis acid.[17] In order to fully evaluate the applicability of this three-component approach to reducing glycals, we optimized the reaction conditions, particularly

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(1) For the employment of chiral building blocks from natural sources see: (a) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon: Oxford, 1983. (b) Seebach, D.; Hungerbuhler, E. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle Sauerlander: Arau, 1980; p 91.

(2) Butterworth, R. F.; Hanessian, S. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 229.

(3) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

(4) Szareck, W. A. *Adv. Carbohydr. Chem. Biochem.* **1973**, *28*, 225.

(5) (a) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. (b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc.* **1969**, 570. (c) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1969**, *24*, 199.

(6) Grinkiewicz, G. *Carbohydr. Res.* **1984**, *128*, C9.

(7) Fraser-Reid, B.; Tam, S. Y.-K.; Radatus, B. *Can. J. Chem.* **1975**, *53*, 2005.

(8) The method has been extensively used as a general method for nucleophilic allylic substitution by variety of carbon nucleophiles,[29] as well as sulfur,[30] oxygen,[53] nitrogen,[54] and phosphorus[55] nucleophiles.

(9) Guthrie, R. D.; Irvine, R. W.; Jenkins, I. D. *Aust. J. Chem.* **1980**, *33*, 2499.

(10) Ogihara, T.; Mitsunobu, O. *Tetrahedron Lett.* **1983**, *24*, 3505.

(11) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314.

(12) Cheng, J. C.-Y.; Daves, G. D., Jr. *Organometallics* **1986**, *5*, 1753 and references cited therein.

(13) Czernecki, S.; Gruy, F. *Tetrahedron Lett.* **1981**, *22*, 437.

(14) Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **1979**, *44*, 3448.

(15) (a) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2814. (b) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89.

(16) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642.

(17) Keinan, E.; Greenspoon, N. *Isr. J. Chem.* **1984**, *24*, 82.

0022-3263/88/1953-3723$01.50/0

with respect to the palladium catalyst, the Lewis acid, and the solvent.

We first attempted to enhance the catalytic activity of palladium for allylic reduction by investigating various phosphine ligands. Assuming that oxidative addition of the allylic acetate to Pd(0) represents the rate-determining step, we employed electron-donating ligands, which increase palladium nucleophilicity. Moreover, by increasing electron density on the palladium, dissociation[18] of phosphine ligands from the metal should be promoted, increasing its propensity to undergo oxidative addition. As our probe, we chose the reduction of cinnamyl acetate with 1,1,3,3-tetramethyldisiloxane in C_6D_6 (where reactions could be conveniently monitored by ^1H NMR) in the presence of 10 mol % of a Pd(0) complex. The relative order of reactivity of the six catalysts examined is represented by the time (minutes, given in parentheses) required to achieve 50% conversion.[19] The results were

$$[Pd[P(p\text{-anisyl})_3]_4\ (16) > Pd[P(p\text{-tolyl})_3]_4\ (18.5) > Pd(PPh_3)_3]_4\ (24) > Pd[P(p\text{-chlorophenyl})_3]_4\ (29) > \tfrac{1}{2}Pd_2(dba)_3 + 4PPh_3\ (125) > Pd[P(p\text{-cyanophenyl})_3]_4\ (\text{no reaction})$$

As expected, electron-donating ligands increase reaction rates. However, probably due to enhanced dissociation, they also destabilize the catalyst and reduce its useful lifetime. Accordingly, employment of acceptor ligands, such as dibenzylideneacetone (dba) and tris(*p*-cyanophenyl)phosphine, effectively stabilize the complex but inhibit catalytic activity. Thus, tetrakis[tri-*p*-tolylphosphine]palladium was found to be the optimal catalyst for our reactions, reaction rates being approximately 1.5 times faster than with $Pd(PPh_3)_4$. Nevertheless, due the generally short reaction times, we employed the latter in most of our reactions.

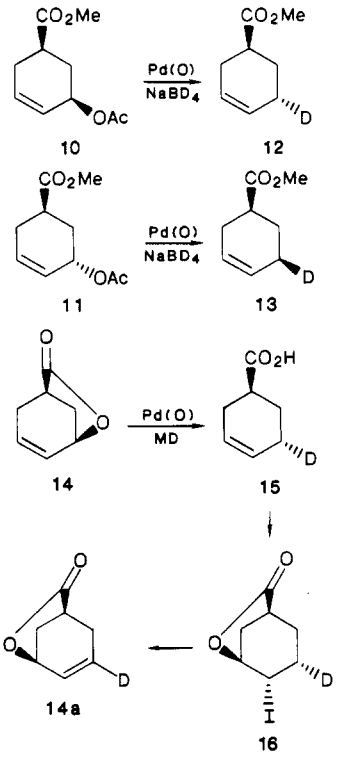
Of the number of Lewis acid cocatalysts examined, we found that $ZnCl_2$ is the most effective for reduction of acetylated glycal derivatives. In fact, Lewis acids frequently employed in the Ferrier reaction,[5] including $BF_3{\cdot}OEt_2$ and $SnCl_4$, were ineffective. Other common Lewis acids, $MgBr_2$, ZnF_2, $Zn(OAc)_2$, ZnI_2, $ZnBr_2$, Al(O-*i*-Pr)$_3$, $CdCl_2$, and Et_2AlCl, were all much less effective than $ZnCl_2$.

The solvent employed was crucial for the reduction. Use of a coordinating solvent (THF, for example) appears to be essential. With the noncoordinating solvent CH_2Cl_2, reactivity of $ZnCl_2$ is much too high,[20] leading to **9**, the product of pure Lewis acid-catalyzed reduction of **1**. This product is formed in the absence of the Pd catalyst, and is known to be produced by reduction with $BF_3{\cdot}OEt_2$ and Et_3SiH.[6]

A number of 3-acetoxyglycal substrates were successfully deoxygenated under the above-recommended set of conditions (Ph_2SiH_2, $Pd[P(p\text{-tolyl})_3]_4$ and $ZnCl_2$ in THF) to yield the corresponding 3-deoxyglycals (Table I).

Stereospecificity. Several years ago we studied the stereochemistry of Pd-catalyzed allylic reduction with $NaBD_4$, employing indicator substrates **10** and **11** (Scheme I).[21] In both cases we observed absolute inversion of configuration at carbon, compounds **12** and **13** being formed, respectively.[22] Since oxidative addition of allylic acetates to Pd(0) occur with inversion of configuration at carbon,[23] the latter results imply that hydride is initially transferred to palladium and from there to the allylic ligand by either migratory insertion or reductive elimination.[21]

Scheme I

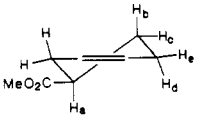


However, similar experiments carried out with the milder hydride donors tributyltin deuteride and dideuteriodiphenylsilane produced a nonreproducible mixture of isomers **12** and **13** from either **10** or **11**. It appeared that reductions with either tin or silicon hydride were slower than those with borohydride, allowing for a significant Pd(0)-catalyzed equilibration[24] of substrates **10** and **11** prior to reduction. We, therefore, turned to lactone **14**,[25] which also possesses a stereochemically defined cis configuration but which cannot epimerize under the reaction conditions to the trans isomer. We studied the palladium-catalyzed reduction of **14** with either $NaBD_4$ or dideuteriodiphenylsilane (in general, MD) with and without zinc chloride.

Although reduction proceeded with variable rates and yields, only one, stereochemically pure product, **15**, was formed in all cases. The relative trans configuration was elucidated by transformation of **15** to its corresponding iodo lactone **16**, followed by dehydroiodination with DBN

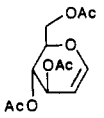
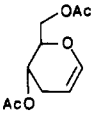
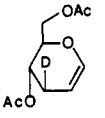
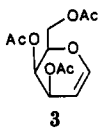
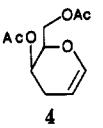
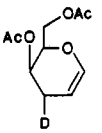
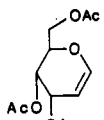
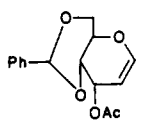
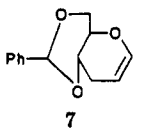
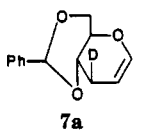
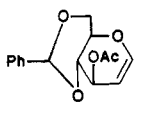
(18) Tolman, C. A.; Seidel, W. C.; Gerlach, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 2669.
(19) This study was carried out in collaboration with Doron Eren of these laboratories.
(20) Mayr, H.; Striepe, W. *J. Org. Chem.* **1985**, *50*, 2995.
(21) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1984**, *23*, 241.

(22) The assignment of the configurations of **12** and **13** was based on ^1H NMR spectra.[56] In the nondeuteriated compound (see structure below) H_b absorbs at 1.68 ppm (dddd, $J_{b,c}$ = 13.5 Hz, $J_{b,a}$ = 11.5 Hz, $J_{b,d}$ = 9.0 Hz, and $J_{b,e}$ = 6.7 Hz). In **12** this absorption changes to dddt (13.5, 11.5, 6.7, 1.4 Hz, respectively), whereas in **13** the signal of H_b appears as a broad quartet with an average coupling constant of approximately 11 Hz.



(23) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.
(24) Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558.
(25) (a) Trost, B. M.; Murphy, B. J. *Organometallics* **1985**, *4*, 1143. (b) Negishi, E.-I.; John, R. A. *J. Org. Chem.* **1983**, *48*, 4098.

Table I. Pd(0)-Catalyzed Allylic Reduction of Glycal Derivatives[a]

entry	starting material	mmol	Ph_2SiH_2, mmol	$ZnCl_2$, mmol	time, h	product	yield, %
1	 1	0.29	1.16	0.63	24	 2	58
2	1	0.33	0.86[b]	1.8	24	 2a	59
3	 3	0.56	0.97	1.99	120	 4	26
4	3	0.27	0.72[b]	2.27	80	 4a	10
5	 5	0.26	1.0[b]	2.0	24	2a	42
6	 6	0.17	0.56	0.85	10	 7	63
7	6	0.17	0.63[b]	2.88	10	 7a	55
8	 8	0.17	0.56	0.85	120	no reaction	

[a] All reactions were carried out in THF at room temperature employing 10 mol % of Pd(0) catalyst according to the general procedure. [b] Dideuteriodiphenylsilane was employed instead of diphenylsilane.

to give **14a**, both processes known to occur with trans stereochemistry.[26] The NMR spectrum of **14a** indicated quantitative incorporation of deuterium at the olefinic position 5 (compared with the spectrum of the nondeuteriated lactone **14**).

The above-described experiments unequivocally showed that hydride transfer to an allylic ligand occurs from the same face of palladium, independent of the source of the hydride, and is therefore a general phenomenon.[27] It was thus surprising to find that reduction of tri-*O*-acetylglucal with $Pd(0)/Ph_2SiD_2/ZnCl_2$ proceeded with the reverse stereospecificity, yielding product **2a** with total retention of configuration at carbon (Table I, entry 2). This rather

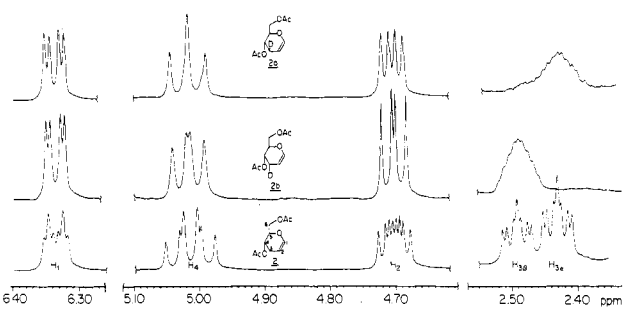
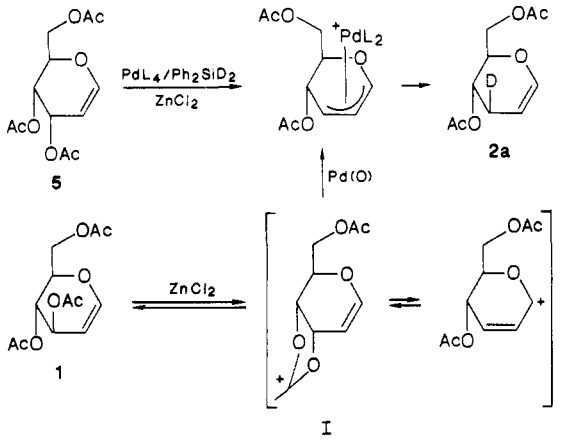


Figure 1. Partial ^1H NMR spectra of 3-deoxyglucals **2a**, **2b**, and **2**. Compound **2a** (upper spectrum) was obtained from **1** by reduction with $Ph_2SiD_2/Pd(0)/ZnCl_2$. Compound **2b** (middle spectrum) was obtained from **17** by reduction with $LiAlD_4$. Compound **2** (lower spectrum) was obtained from **1** by reduction with $Ph_2SiH_2/Pd(0)/ZnCl_2$.

(26) (a) Grew, R.; Heinke, A.; Sommer, C. *Chem. Ber.* **1956**, *89*, 1978. (b) Kato, M.; Kageyama, M.; Tanaka, R.; Kuwahara, K.; Yoshikoshi, A. *J. Org. Chem.* **1975**, *40*, 1932.

(27) Reduction of dimeric, neutral π-allylpalladium complexes with $LiAlH_4$ proceeds with the same stereochemistry. See: (a) Jones, D. N.; Knox, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 165. (b) Backvall, J. E.; Nordberg, R. E.; Bjorkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943.

Scheme II



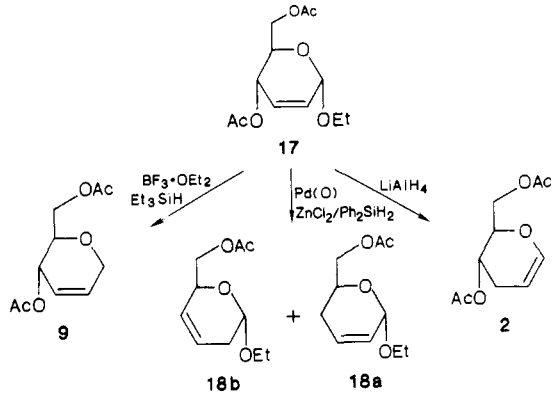
unusual stereospecificity of the reduction of **1** was also observed with other deuteride sources, such as $NaBD_4$ and tributyltin deuteride, albeit with somewhat lower chemical yields. The configuration of **2a** at position 3 was confidently assigned by ^1H NMR from the known characteristics of allylic systems, in which $J_{1,3_a}$ is larger than $J_{1,3_e}$ and $J_{2,3_a}$ is smaller than $J_{2,3_e}$.[28] Also, $J_{3_a,4_a}$ is larger than $J_{3_e,4_a}$. Further support for this interpretation was provided by comparing the spectrum of **2a** to that of its known epimer **2b**[7] (Figure 1).

We suspected that the stereochemistry of the reduction of **1** represents an exceptional case arising from participation of the 4-acetoxy substituent in the dissociation of the allylic 3-acetoxy group.[29f,5c,30] To check this hypothesis, we examined the stereochemistry of the reduction of tri-*O*-acetylallal **5** (Table I, entry 5) and found that reduction of both **1** and **5** with Ph_2SiD_2 cleanly produces the same stereoisomer **2a**. This observation indeed supports the involvement of a stabilized carbonium intermediate I, which is the actual substrate for the Pd-catalyzed reduction of **1**, formation of the π-allylpalladium complex at the top face of the sugar ring occurring with both **1** and **5** (Scheme II). Thus, although reduction of **1** exhibits an exceptional overall stereospecificity, the actual reduction step involves a normal, direct transfer of hydride from palladium to the substrate.

Intermediate I is much more reactive toward Pd(0) than **1**, not only because it contains a positively charged leaving group but also because the leaving group in I is pseudoaxial,[31] as compared to its pseudoequatorial conformation in **1**. Conformation of the leaving group in these reactions appears to be crucial, as demonstrated by two benzylidene derivatives, **6** and **8**, which were prepared from glucal and allal, respectively. No reaction was observed with **8**, where the allylic acetate is locked into a pseudoequatorial conformation, whereas compound **6**, with allylic acetate locked into a pseudoaxial conformation, was completely reduced to **7** under the same conditions (see Table I, entries 6–8).

The rather slow reduction rates and poor yields observed in the case of tri-*O*-acetylgalactal **3** (Table I, entries 3, 4) may be understood from the above discussion. The preferred conformation of the leaving group in **3** is pseudoequatorial,[32] as in glucal **1**. However, in contrast to the latter, the 4-acetoxy group in **3** is cis to the leaving group, rendering anchimeric assistance impossible and resulting in poor reactivity of this substrate toward Pd(0).

Scheme III



2,3-Unsaturated Monosaccharides. Lewis acid catalyzed reduction involving an allylic carbonium intermediate at the anomeric position generally results in the corresponding 2,3-unsaturated derivative,[6] irrespective of the original location of the leaving group. For example, reduction of either tri-*O*-acetylglucal (**1**) or ethyl-4,6-di-*O*-acetyl-Δ^2-glucopyranoside (**17**) with $BF_3{\cdot}OEt_2$ and Et_3SiH, yields **9** as the sole product.[6] Complementary regioselectivity is achieved when substitution by hydride is carried out under basic conditions. For example, reduction of **17** with $LiAlH_4$[7] (Scheme III) yields 3-deoxyglucal **2** exclusively.

When employing our three-component reducing system, reduction of **17** proceeds with regioselectivity that differs from both these just described reactions. Due to the difficulty in forming a π-allylpalladium complex including the anomeric position, the normally less reactive 4-position is chemoselectively activated,[33] leading to formation of a mixture of **18a** and **18b** in a 1:3 ratio. The generality of this selectivity is demonstrated by examples given in Table II.

As expected, because formation of a π-allylpalladium intermediate across positions 2, 3, and 4 is easier than that at positions 1, 2, and 3 (vide infra), reaction rates and yields in Table II are generally higher than those given in Table I. An interesting feature of the reductions shown in Table II is the regioselectivity of hydride addition. The ratio of products, 2,3- and 3,4-unsaturated derivatives a and b ranges from 1:3 up to 1:1. From the limited number of examples studied, it is difficult to draw clear conclusions. Yet, it appears that the regiochemistry of reduction is more sensitive to the substituent at the anomeric position than it is to the substituent at the 5-position.

Synthetic Applications. The need for convenient synthetic routes to 3-deoxyglycals mainly arises from the access provided by the latter to a wide variety of 3- and 2-deoxysaccharides.[34] For example, compounds **2a** and **2b** are useful starting materials for the synthesis of 2(*S*)- and 2(*R*)-deuterio-2-deoxy-D-*erythro*-pentoses, respectively.[35] These stereospecifically labeled deoxyriboses were used for determination of stereochemistry in the biosynthesis of deoxyribonucleotides from ribonucleotides.[36]

(28) Garbish, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561.
(29) (a) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180. (b) Dawe, R. D.; Fraeser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522. (c) Grynkiewicz, G.; Zamojsky, A. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1980**, *35B*, 1024. (d) Grynkiewicz, G.; Bemiller, J. N. *J. Carbohydr. Chem.* **1982**, *1*, 122. (e) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 3803. (f) Heynes, K.; Park, J. I. *Chem. Ber.* **1976**, *109*, 3262.
(30) Priebe, W.; Zamojski, A. *Tetrahedron* **1980**, *36*, 287.
(31) Fiaud, J. C.; Aribi-Zouioueche, L. *J. Chem. Soc., Chem. Commun.* **1986**, 390.
(32) Rico, M.; Santoro, J. *Org. Magn. Reson.* **1976**, *8*, 49.
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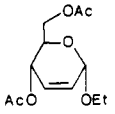
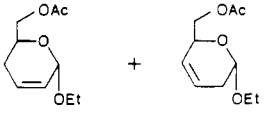
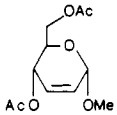
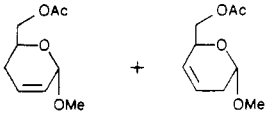
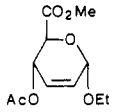
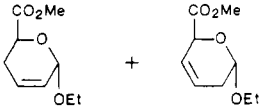
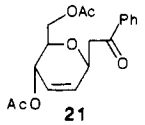
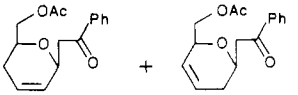
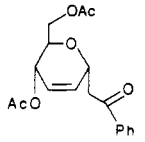
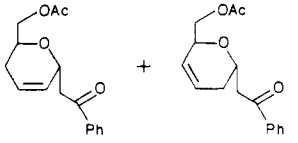
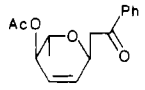
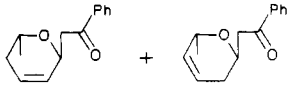
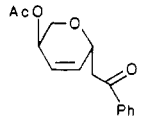
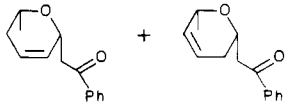
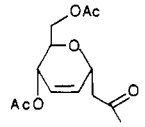
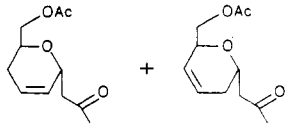
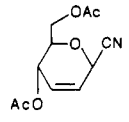
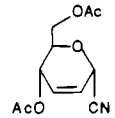
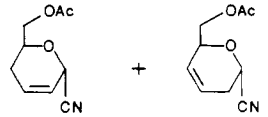
Table II. Pd(0)-Catalyzed Allylic Reduction of 2,3-Unsaturated Sugar Derivatives[a]

entry	starting material	mmol	Ph_2SiH_2, mmol	$ZnCl_2$, mmol	time, h	products	yield, %
1	 **17**	0.27	0.67	0.57	2	 **18a** (33:67) **18b**	75
2	 **19**	0.88	1.52	1.76	3	 **28a** (25:75) **28b**	55
3	 **20**	0.38	0.78	0.7	3	 **29a** (44:56) **29b**	92
4	 **21**	0.45	0.72	1.1	6	 **30a** (50:50) **30b**	91
5	 **22**	0.46	0.63	1.1	4	 **31a** (50:50) **31b**	94
6	 **23**	0.18	0.5	0.78	2	 **32a** (50:50) **32b**	82
7	 **24**	0.17	0.5	0.41	4	 **33a** (50:50) **33b**	79
8	 **25**	0.3	0.6	0.73	4	 **34a** (50:50) **34b**	65
9	 **26**	0.3	0.6	0.73	4	 **35a** (50:50) **35b**	68
10	 **27**	0.32	0.65	0.6	5	 **36a** (75:25) **36b**	63

[a] All reactions were carried out in THF at room temperature employing 10 mol % of Pd(0) catalyst according to the general procedure.

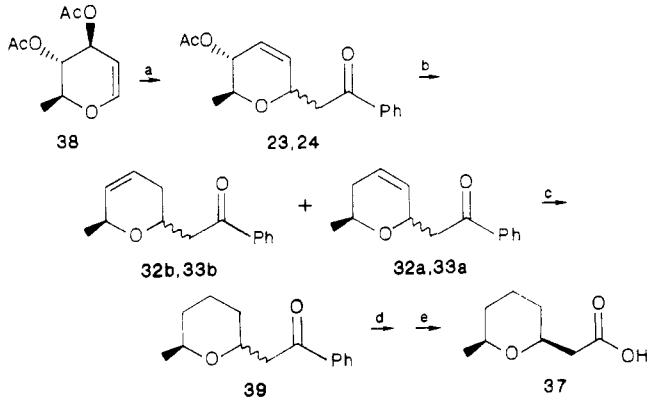
While **2b** is easily obtainable in one step from a readily available substrate,[7] previous syntheses of **2a** required a multistep approach to its precursor, methyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranoside.[7,37] Therefore, our palladium-catalyzed allylic reduction of commercially available **1** represents an attractive synthesis of **2a**.

Scheme IV outlines the employment of another deoxygenated sugar molecule as a chiral building block in the

(36) Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1971**, *93*, 6342.

(37) Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61.

Scheme IV. Total Synthesis of (+)-(2*S*,6*S*)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid (37)[a]



[a] Key: (a) α-(trimethylsiloxy)styrene, BF_3·OEt_2, CH_2Cl_2, −45 °C to room temperature, 80%; (b) $Pd(PPh_3)_4$ (10 mol %), Ph_2SiH_2, $ZnCl_2$, 80%; (c) $RhCl(PPh_3)_3$, H_2, EtOH, 90%; (d) $PhCO_2H$, $CHCl_3$, reflux 16 h, 100%; (e) (1) CF_3CO_3H, CH_2Cl_2, Na_2HPO_4, 0 °C, 3 h; (2) NaOH, MeOH, overall 94–98%.

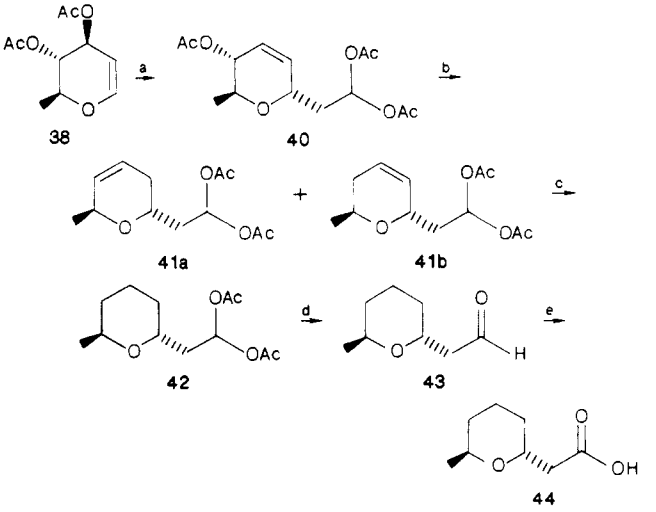
total synthesis of (+)-(2*S*,6*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**37**), a naturally occurring heterocyclic acid found in trace quantities in the perfume material secreted by the scent gland of the civet cat (*Viverra civetta*).[38]

The first step of the synthesis involved Lewis acid catalyzed condensation of the silyl enolate of acetophenone and di-*O*-acetylrhamnal **38**,[39] resulting in equal quantities of the two anomeric epimers **23** and **24**.[29b] Although these isomers are separable by flash chromatography, their isolation was unnecessary, as both were easily equilibrated at a later stage of the synthesis. Palladium-catalyzed allylic reduction of these 2,3-unsaturated sugar derivatives proceeded in 80% isolated yield, affording a mixture of four isomers **32a**, **32b**, **33a**, and **33b** in approximately equal amounts. The possibility to reduce allylic acetates save the need for the three-step sequence which was required in order to remove an oxygen function in a related synthesis of **37** by first hydrolysis of the acetate than conversion to the allylic chloride and only then reducing with $LiAlH_4$.[40] Homogeneous catalytic hydrogenation over Wilkinson catalyst[41] afforded the desired tetrahydropyranyl structure **39** in 90% yield. Acid-catalyzed equilibration of the two anomeric epimers, followed by Baeyer-Villiger oxidation with trifluoroperacetic acid and basic hydrolysis of the resultant phenyl ester, was carried out according to our previous report, with excellent yields.[38] The final product, **37**, was identical (NMR, IR, MS, $[\alpha]_D$) with an authentic sample from our previous syntheses.[38,42]

Another approach to the above described natural product is demonstrated by the total synthesis of its thermodynamically less stable isomer, (2*R*,6*S*)-(*trans*-6-methyltetrahydropyran-2-yl)acetic acid (**44**)[38,42] (Scheme V).

1-(4′-Acetoxy-2′,3′,6′-trideoxy-D-β-*threo*-hex-2′-enopyranosyl)-2,2-diacetoxyethane (**40**) was easily prepared from di-*O*-acetylrhamnal **38**.[29d] Reductive cleavage of the

Scheme V. Total Synthesis of (+)-(2*R*,6*S*)-(*trans*-6-Methyltetrahydropyran-2-yl)acetic Acid (44)[a]



[a] Key: (a) vinyl acetate, $FeCl_3$, CH_2Cl_2, 0 °C, 30 min, 70%; (b) $Pd(PPh_3)_4$ (10 mol %), Ph_2SiH_2, $ZnCl_2$, 87%; (c) Pt/C (10%), H_2 (1 atm), EtOH, 99%; (d) NaOMe, MeOH, 5 min; (e) Jones reagent, acetone, 70%.

allylic acetate of **40** proceeded in excellent yield (87%) to give a 1:1 mixture of the two dihydropyran isomers **41a** and **41b**. Hydrogenation of this mixture with catalytic amounts of platinum on charcoal under 1 atm of hydrogen produced (2*R*,6*S*)-*trans*-2-(2′,2′-diacetoxyethyl)-6-methyltetrahydropyran (**42**) in essentially quantitative yield. Methanolic sodium methoxide hydrolyzed the geminal diacetoxy groups of **42** to the corresponding aldehyde **43** in 60% yield. The latter was finally oxidized with Jones reagent to the carboxylic acid **44** in 80% yield. This compound was found to be identical (^1H NMR, ^{13}C NMR, IR, MS, optical rotation) to an authentic sample synthesized earlier in these laboratories.[38,42]

Conclusion

Highly chemoselective reductive cleavage of allylic acetates of 1,2- and 2,3-unsaturated monosaccharides was achieved by a three-component reducing system comprised of diphenylsilane, a soluble palladium(0) catalyst, and catalytic amounts of zinc chloride. It was demonstrated that substitution by hydride proceeds with absolute inversion of the configuration at carbon, implying that hydride is initially transferred to palladium and from there to the allylic ligand. This stereospecificity may be modified in cases where anchimeric assistance is possible. The usefulness of the new chiral building blocks thus formed was demonstrated by the total synthesis of the civet constituent, (+)-(2*S*,6*S*)-*cis*-(6-methyltetrahydropyran-2-yl)-acetic acid as well as its (+)-2*R*,6*S*-trans isomer. Other natural products are currently being synthesized in our laboratories, employing chirons derived from unsaturated sugar derivatives.

Experimental Section

General Methods. Elemental analyses were carried out at the microanalytical laboratory of the Hebrew University, Jerusalem. Infrared spectra were measured on the neat compounds with an FT infrared CYGNUS 25, Mattson Instruments, and are given in cm^{-1} units. Patterns are designated as follows: br, broad; sh, shoulder; s, strong; w, weak; m, medium. ^1H NMR spectra were measured in deuteriochloroform (unless otherwise cited) on a Varian FT-80A or a Bruker WH-270 NMR spectrometer. All chemical shifts are reported in δ units downfield from Me_4Si, and

(38) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474 and references cited therein.
(39) Roth, W., Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405.
(40) Lichtenthaler, F. W.; Klingler, F. D.; Jarglis, P. *Carbohydr. Res.* **1984**, *132*, C1.
(41) Rylander, P. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, 1979; pp 51–58.
(42) Keinan, E.; Seth, K. K.; Sahai, M.; Berman, E. *J. Org. Chem.* **1986**, *51*, 4288.

the J values are given in hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High-resolution mass spectra were recorded on a Varian MAT-731 spectrometer. GC–MS analysis were carried out with, a Finnigan 4500 instrument. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art 5549). Column chromatography separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under a pressure of 0.4 atm (flash chromatography). Distillations were usually performed with a Buchi Kugelrohr apparatus, and the temperatures given are pot temperatures. Tetrahydrofuran and diethyl ether were distilled over sodium benzophenone ketyl. Tetrakis(triarylphosphine)-palladium(0) complexes were prepared from $PdCl_2$ and the appropriate phosphine.[43]

Starting Materials. The following monosaccharide substrates were prepared according to the cited references: tri-*O*-acetylglucal **1**;[39] tri-*O*-acetylgalactal **3**;[44] di-*O*-acetylrhamnal **38**;[39] tri-*O*-acetylallal **5**;[45] 4,6-*O*-benzylidene-D-glucal **8**;[46] 4,6-*O*-benzylidene-D-allal **6**;[37] ethyl and methyl 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside (**17** and **19**, respectively);[47] ethyl 3,4-diacetyl-D-glucoronal **20**;[48] β- and α-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-D-*erythro*-hex-2′-enopyranosyl)acetophenone (**21** and **22**, respectively);[29b] α-(4′,6′-di-*O*-acetyl-2′,3′-dideoxy-D-*erythro*-hex-2′-enopyranosyl)acetone (**25**);[29d] and 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl β- and α-cyanide (**26** and **27**, respectively).[49,50]

β- and α-1-(4′-Acetoxy-2′,3′,6′-trideoxy-D-*threo*-hex-2′-enopyranosyl)acetophenone (23 and 24). Preparation according to the literature procedure[29b] afforded a 1:1 mixture of **23** and **24** in 80% yield. These two isomers were separated by flash chromatography using ethyl acetate/hexane (1:10).

23: NMR 7.96 (d, 2 H), 7.55 (t, 1 H), 7.45 (d, 2 H), 6.06 (ddd, J = 10.3, 1.4, 2.5, H2), 5.82 (ddd, J = 10.3, 1.5, 3, H3), 4.90 (ddd, J = 6.6, 4.5, 1.4, H4), 4.86 (m, H1), 3.87 (quintet, J = 6.6, H5), 3.44 (dd, J = 16.5, 6.8, H7), 3.13 (dd, J = 16.5, 6.6), 2.09 (s, OAc), 1.25 (d, J = 6.6); IR 2980, 2935, 2868, 1737, 1686, 1598, 1449, 1395, 1373, 1347, 1277, 1238, 1202, 1135, 1109, 1066, 1045, 1025, 1003, 753, 691. MS, m/e (relative intensity) 230 (19), 214 (34), 199 (47), 188 (29), 120 (17), 106 (49), 105 (100), 95 (80), 83 (16), 78 (10), 77 (99), 43 (100); HRMS, 214.1030 (M^+ – AcOH), calcd for $C_{14}H_{14}O_2$ 214.0994. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.52; H, 6.53. $[\alpha]_D$ −105° (c 0.60, chloroform).

24: NMR 7.96 (d, 2 H), 7.57 (t, 1 H), 7.46 (d, 2 H), 5.94 (dt, J = 10.3, 1.5, H2), 5.73 (dt, J = 10.3, 1.5, H3), 5.06 (dm, J = 9.6, 1.5, H4), 4.81 (m, H1), 3.63 (dq, J = 9.6, 6.3, H5), 3.36 (dd, J = 16.7, 7.1, H7), 3.03 (dd, J = 16.7, 7.1), 2.1 (s, OAc), 1.22 (d, J = 6.3, H6); IR 2980, 2937, 1735, 1685, 1598, 1450, 1374, 1276, 1240, 1205, 1195, 1100, 1072, 1044, 1024, 1003, 754; MS, m/e (relative intensity) 230 (42), 214 (43), 199 (59), 188 (57), 120 (11), 106 (72), 105 (100), 95 (50), 83 (24), 81 (12), 78 (16), 77 (100), 50 (13), 43 (100); HRMS, 214.0998 (M^+ – AcOH), calcd for $C_{14}H_{14}O_2$ 214.0994. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.74; H, 6.60. $[\alpha]_D$ −151° (c 0.91, chloroform).

Comparative Study of Catalysts. $Pd(PAr_3)_4$ (0.01 mmol) was added to a solution containing cinnamyl acetate (17.6 mg, 0.1 mmol) and 1,1,3,3-tetramethyldisiloxane (16.1 mg, 0.12 mmol) in C_6D_6 (0.5 mL). Conversion rates were determined by following the disappearance of cinnamyl acetate (integration of the signals at 6.40 and 4.57 ppm) and the appearance of 1-phenylpropene and allylbenzene (signals at 6.34 and 3.17 ppm, respectively). The following reaction times were required to achieve 50% conversion: (a) Ar = 4-methoxyphenyl, 16 min; (b) Ar = p-tolyl, 18.5 min; (c) Ar = phenyl, 24 min; (d) Ar = 4-chlorophenyl, 29 min; (e) Ar = 4-cyanophenyl, no reaction after 10 h; (f) with combination of $Pd_2DBA_3{\cdot}CHCl_3$ (5 mg, 10 mol % Pd) and PPh_3 (10.5 mg, 40 mol %), 125 min.

General Procedure for Allylic Reductions of Unsaturated Monosaccharides. Palladium–tetrakis(tri-p-tolylphosphine) (10 mol %) was added to a 5-mL THF solution containing the substrate (0.17–0.56 mmol), diphenylsilane (2–4 equiv), and zinc chloride (2–6 equiv). In the cases of ethyl or methyl glycosides **17**, **19**, and **20**, the appropriate alcohol, either ethanol or methanol (10 equiv), was added. The mixture was stirred at room temperature until no starting material could be detected by TLC (reactions carried out with $Pd(PPh_3)_4$ as catalyst were approximately 30% slower). The mixture was filtered over short silica gel column using CH_2Cl_2, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography. More details are given in Tables I and II.

The known products **2**, **2a**, **4**, **4a**, **7**, **7a**,[7] **18a**, **18b**, **28a**, **28b**, **29a**,[51] and **29b**[52] were compared those in the literature. In particular, using the PANIC simulation program (version 820601, performed with a Bruker Aspect 2000), we reproduced the literature NMR spectra from the reported data and compared them to the spectra of our products. Compound **2b** was prepared by reduction of **1** with $LiAlD_4$ according to the procedure of Fraiser-Reid.[7]

Stereochemical Studies. A. Reduction of *cis*- and *trans*-3-Acetoxy-5-carbomethoxycyclohex-1-ene (10 and 11). $NaBD_4$ (35 mg, 0.83 mmol) was added to a stirred solution containing **10** (37 mg, 0.19 mmol) and $Pd(PPh_3)_4$ (148 mg, 0.12 mmol, 67 mol %) in THF (5 mL). Progress of the reaction was followed by GC. After 1 h, NH_4Cl was added and the reaction mixutre was filtered over a short silica gel column with CH_2Cl_2. The solvent was removed under reduced pressure, and the product was purified by preparative GC, affording **12**, which was found to be pure by ^1H NMR.[22] Similar reduction of **11** yielded pure **13**.[22]

B. Conversion of Lactone 14 into 14a. (a) $Pd(PPh_3)_4$ (47 mg, 44 mol %) was added to a THF (5 mL) solution containing **14** (96 mg, 0.9 mmol), dideuteriodiphenylsilane (244 mg, 1.3 mmol), and zinc chloride (189 mg, 1.4 mmol). The mixture was stirred at room temperature for 16 h, after which no starting material could be detected by TLC. It was then filtered over a short silica gel column with dichloromethane, and the solvent was removed under reduced pressure. The product was Kugelrohr distilled [130 °C (0.2 mm)], affording 1-carboxy-5-deuteriocyclohex-3-ene (**15**) (50 mg, 52% yield).

(b) Iodolactonization of **15** to **16** was carried out as reported[26a] with iodine (200 mg), potassium iodide (780 mg) in water (2.5 mL) and a 0.5 N sodium bicarbonate solution (5 mL).

(c) Dehydroiodination[26b] of **16** to **14a** was carried out in benzene (5 mL) by using DBN (60 mg). The crude deuterio lactone **14a** was purified by Kugelrohr distillation.

14a: NMR 6.23 (m, 1 H), 4.77 (t, J = 6 Hz, 1 H), 2.91 (m, 1 H), 2.50 (m, 3 H), 2.08 (d, J = 12 Hz, 1 H). Traces of the non-deuteriated lactone **14** (<5%) was detected in the NMR spectrum (a low intensity multiplet at 5.58 ppm).

Identical results were obtained in a similar experiment where zinc chloride was omitted from the reaction mixture. Same results were also obtained with $NaBD_4$ instead of diphenylsilane and zinc chloride.

Compounds 30a and 30b. Reduction of **21** was performed following to the general procedure, the crude mixture was flash chromatographed by using ethyl acetate/hexane (1:4), affording a mixture of **30a** and **30b** in a 1:1 ratio.

30a: NMR 5.88–5.74 (m, H2, H3), 4.79 (m, H1), 4.05 (m, H6, H6′), 3.86 (dt, J = 15.2, 5, H5), 3.34 (dd J = 16.4, 6.1, H7), 3.02 (dd, J = 16.4, 7.3, H7′), 2.1–1.9 (m, H4, H4′).

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30b: NMR 5.91 (ddt, J = 10.2, 5, 2.4, H3), 5.60 (ddt, J = 10.2, 2.6, 1.3, H4), 4.39 (m, H5), 4.23 (m, H1), 4.05 (m, H6, H6'), 3.42 (dd, J = 16.3, 6.4, H7), 2.99 (dd J = 16.3, 6.1, H7'), 2.1–1.9 (m, H2, H2').

Mixture of **30a** and **30b**: IR 3070, 2944, 2939, 1741, 1736, 1686, 1683, 1597, 1443, 1430, 1369, 1238, 1187; MS, m/e (relative intensity) 274 (M^+, 4), 214 (14), 201 (9), 162 (9), 147 (12), 120 (23), 106 (29), 105 (100), 95 (39), 94 (100), 82 (12), 81 (100), 78 (11), 77 (93), 67 (17), 66 (14), 65 (9); HRMS, 274.1187 (M^+), calcd for $C_{16}H_{18}O_4$ 274.1205. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.72; H, 6.32.

Compounds 31a and 31b. Reduction of **22** was performed following the general procedure. Flash chromatography with ethyl acetate/hexane (1:8) afforded compounds **31a** and **31b** as an inseparable mixture.

31a: NMR 5.85 (m, H2, H3), 4.91 (m, H1), 4.07 (m, H6, H6'), 4.02 (m, H5), 3.4 (dd, J = 15.7, 7.5, H7), 3.07 (dd, J = 15.7, 6.2, H7'), 2.15–1.95 (m, H4, H4').

31b: NMR 5.95 (ddd, J = 9.4, 5, 2.1, H3), 5.65 (ddt, J = 9.4, 3.4, 1.3, H4), 4.38 (m, H5), 4.37 (m, H1), 4.07 (m, H6, H6'), 3.34 (dd, J = 16.1, 6.4, H7), 3.02 (dd, J = 16.1, 6.4, H7'), 2.22 (dddd, J = 15, 13, 5, 4, H2), 2.15 (1.95 m, H2').

Mixture of **31a** and **31b**: MS, m/e (relative intensity) 274 (M^+ 3), 216 (13), 214 (11), 201 (13), 154 (13), 147 (9), 139 (32), 120 (9), 106 (20), 105 (100), 95 (42), 94 (62), 82 (14), 81 (100), 78 (11), 77 (70), 67 (18), 66 (9); HRMS, 274.1297 (M^+), calcd for $C_{16}H_{18}O_4$ 274.1205; 214.1031 (M^+ – AcOH), calcd for $C_{14}H_{14}O_2$ 214.0994. IR 3070, 2944, 1739.9, 1682.0, 1597.6, 1449.4, 1429.8, 1367.4, 1279.6, 1238.3, 1187.5, 1124.0, 1118, 1088, 1069, 1046.

Compounds 32a and 32b. Reduction of **23** by the general procedure, followed by flash chromatography using ethyl acetate/hexane (1:10), afforded compounds **32a** and **32b** in a 1:1 ratio.

32a: NMR 5.85–5.75 (m, H2, H3), 4.78 (m, H1), 3.86 (m, H5), 3.39 (dd, J = 15.6, 7.2, H7), 3.11 (dd, J = 15.6, 6.4, H7'), 1.96 (m, H4), 1.19 (d, J = 6.5, CH_3); MS (GCMS), m/e (relative intensity) 216 (5), 120 (6), 105 (100), 97 (54), 96 (23), 81 (11), 79 (11), 77 (58).

32b: NMR 5.83 (m, H3), 5.70 (dm, J = 9.2, H4), 4.38 (m, H1), 4.38 (m, H5), 3.33 (dd, J = 16.3, 6.7, H7), 3.03 (dd, J = 16.3, 6.1, H7'), 2.20 (dm, J = 17.2, H2), 2.06 (m, H2); MS, m/e (relative intensity) 216 (0.6), 147 (12), 120 (25), 105 (84), 96 (52), 95 (20), 81 (100), 77 (73).

Mixture of **32a** and **32b**: IR 3000, 1683, 1597, 1592, 1449, 1119, 1082.

Compounds 33a and 33b. Reduction of **24** by the general procedure, followed by flash chromatography, afforded compounds **33a** and **33b** in a 1:1 ratio.

33a: NMR 5.82–5.70 (m, H2, H3), 4.77 (m, H1), 4.27 (m, H5), 3.36 (dd, J = 16.3, 6.6, H7), 3.02 (dd, J = 16.3, 7.6, H7'), 1.98 (m, 2 H, H4, H4'), 1.18 (d, J = 3.4, 3 H, H6).

33b: NMR 5.75 (m, H3), 5.60 (dm, J = 10, H4), 4.27 (m, H1), 3.72 (q, J = 6.6, H5), 3.39 (dd, J = 16.4, 6.5, H7), 2.99 (dd, J = 16.4, 6.3, H7'), 2.07 (m, 2 H, H2, H2'), 1.20 (d, J = 6.6, CH_3).

Mixture of **33a** and **33b**: IR 2950, 1685, 1449, 1364, 1280, 1217, 1187, 1116, 1090, 1076, 1067, 1050; MS, m/e (relative intensity) 216 (4.1) (M^+), 120 (11), 105 (100), 97 (13), 96 (39), 81 (24), 77 (70), 68 (28), 67 (24).

Compounds 34a and 34b. Reduction of **25** by the general procedure, followed by flash chromatography using ethyl acetate/hexane (1:4), afforded compounds **34a** and **34b** in a 1:1 ratio.

34a: NMR 5.85 (ddt, J = 12.8, 5.7, 1.9, H3), 5.73 (ddd J = 12.8, 2.5, 1.9, H2), 4.71 (m, H1), 4.10 (m, H6, H6'), 3.94 (m, H5), 2.83 (dd, J = 15.3, 8.7, H7), 2.53 (dd, J = 15.3, 5.2, H7'), 2.22 (s, Me), 2.05 (s, OAc), 2.0 (m, H4, H4').

34b: NMR 5.95 (dddd, J = 10.3, 4.9, 2.6, 2.3, H3), 5.66 (ddd, J = 10.3, 4, 1.4, H4), 4.23 (m, H1), 4.37 (m, H5), 4.1 (m, H6, H6'), 2.73 (dd, J = 15.8, 7.5, H7), 2.53 (dd, J = 15.8, 5.1, H7'), 2.20 (s, Me), 2.05 (s, OAc), 2.0 (m, H2, H2').

Mixture of **34a** and **34b**: IR 2924, 1741, 1717, 1431, 1367, 1239, 1120, 1089, 1041, 713; MS, m/e (relative intensity) 212 (M^+ 0.4), 169 (5), 152 (M^+ – AcOH, 11), 134 (4), 111 (5), 110 (5), 109 (11), 96 (7), 95 (93), 94 (76), 83 (6), 82 (6), 81 (58), 79 (14), 68 (12), 67 (100), 66 (33), 65 (11), 55 (16), 53 (18), (CI) 213 (M + 1, 20), 155 (100), 135 (3), 111 (2), 103 (3). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.07; H, 7.21.

Compounds 35a and 35b. Reduction of **26** by the general procedure, followed by flash chromatography using ethyl acetate/hexane (1:4), afforded compounds **35a** and **35b** in a 1:1 ratio.

35a: NMR 6.09 (ddt, J = 10.1, 5.5, 2.6, H3), 5.73 (ddt, J = 10.1, 2.0, 1.0, H2), 5.10 (m, J = 2.6, 2.0, H1), 4.28–4.04 (m, H6, H6'), 3.85 (ddt, J = 6.4, 6.2, 3.1, H5), 2.36–2.07 (m, H4, H4'), 2.10 (s, OAc); IR 3000, 1743, 1719, 1701, 1430, 1370, 1237, 1126, 1121, 1090, 1052; MS (CI), m/e 182 (M + 1), 155 (M^+ – CN).

35b: NMR 5.95 (ddt, J = 10.5, 4.9, 2.3, H3), 5.70 (ddt, J = 10.5, 2.3, 1.0, H4), 4.52 (dd, J = 9.8, 3.9, H1), 4.46 (m, J = 5.6, 1.0, H5), 4.16 (d, J = 5.6, H6, H6'), 2.62 (tdd, J = 9.8, 4.9, 2.3, H2), 2.35 (dddd, J = 9.8, 2.3, 3.9, 1.0, H2'), 2.10 (s, OAc); IR 2950, 1742, 1431, 1395, 1385, 1369, 1236, 1201, 1189, 1119, 1080, 1045; MS (CI), m/e 182 (M + 1), 155 (M^+ – CN).

Compounds 36a and 36b. Reduction of **27** by the general procedure, followed by flash chromatography using ethyl acetate/hexane (1:2), afforded compounds **36a** and **36b** in a 1:2 ratio.

36a: NMR 6.08 (ddt, J = 9.9, 5.2, 2.1, H3), 5.73 (dm, J = 9.9, H2), 5.03 (m, H1), 4.15 (m, H6, H6'), 4.05 (m, H5), 2.13 (m, H4, H4'), 2.10 (s, OAc).

36b: NMR 5.95 (ddt, J = 10.2, 4.8, 2.3, H3), 5.73 (dm, J = 10.2, 1, H4), 4.89 (dd, J = 6.1, 2.1, H1), 4.60 (m, J = 5, 2.3, 1, H5), 4.15 (m, J = 5, 2 H, H6, H6'), 2.65 (ddt, J = 17.8, 5.2, 3.4 Hz, H2), 2.26 (dm, J = 17.8, 3.8, 2.3 Hz, H2'), 2.10 (s, OAc).

Mixture of **36a** and **36b**: IR 2950, 2130 (vw), 1739, 1432, 1370, 1232, 1189, 1097, 1047; MS (CI), m/e 182 (M + 1), 155 (M^+ – CN). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 60.06; H, 6.00; N, 6.98.

***cis*- and *trans*-(6*S*)-(6-Methyltetrahydropyran-2-yl)-acetophenone (39).** $RhCl(PPh_3)_3$ (10 mg, 0.01 mmol) was added to a solution containing equal proportions of **32** and **33** (60 mg, 0.27 mmol) in EtOH (3 mL), and the mixture was stirred under 1 atm of H_2 for 3 h. The reaction mixture was then filtered through a short column of silica gel with CH_2Cl_2. The solvent was removed under reduced pressure, and the products were further purified by flash chromatography affording **39** (54.5 mg, 90%) as a 1:1 mixture of cis and trans isomers. The latter compounds were identical with authentic samples[38] (NMR, IR, MS, $[\alpha]_D$).

1-(4'-Acetoxy-2',3',6'-trideoxy-D-*β*-*threo*-hex-2'-enopyranosyl)-2,2-diacetoxyethane (40). Compound **40** was prepared according to the known method[29d] in 70% yield.

40: NMR 6.94 (dd, J = 4.7, 6.6, 1 H), 5.87 (dt, J = 10.3, 1.0, H2), 5.78 (dt, J = 10.3, 2.0, H3), 4.89 (dd, J = 2, 3, H4), 4.32 (ddd, J = 2.1, 4.1, 6.2, H1), 3.86 (quintet, J = 6.2, H5), 2.20–1.89 (m, 2 H), 2.07 (OAc), 2.06 (OAc), 1.22 (d, J = 6.2, H6); IR 2979.7, 1760.0, 1743.0, 1432.6, 1375.0, 1235.5, 1202.9, 1039, 1020, 731; MS, m/e (relative intensity) 300 (M^+, 3), 267 (6), 213 (6), 212 (5), 201 (5), 196 (38), 182 (5), 173 (6), 170 (7), 163 (7), 162 (9), 155 (20), 154 (100), 151 (9), 145 (16), 144 (13), 139 (28), 138 (52), 137 (37), 128 (10), 126 (13), 123 (41), 115 (13), 113 (29), 112 (100), 111 (10), 103 (36), 96 (14), 95 (97), 94 (21), 87 (13), 84 (37), 83 (58), 81 (23); $[\alpha]_D$ –56.7° (c 1.5, $CHCl_3$).

(2*R*,6*S*)-*trans*-2-(2',2'-Diacetoxyethyl)-6-methyl-2,3-dihydropyran and -2,5-dihydropyran (41a and 41b). Compound **40** was reduced under our general procedure, followed by purification by flash chromatography with ethyl acetate/hexane (1:6), giving rise to inseparable mixture of **41a** and **41b** in a 1:1 ratio (87% yield).

Mixture of **41a** and **41b**: NMR 6.99 (dd, J = 4.4, 7.3, 1 H), 6.92 (dd, J = 4.4, 6.8, 1 H), 5.63–5.86 (m, vinylic protons), 4.33 (m, H5 of **41b** and H1 of **41a**), 3.83 (m, H5 of **41a** and H1 of **41b**), 2.24–1.82 (m, 6 H), 2.08 (OAc), 2.09 (OAc), 1.21 (d, J = 6.1), 1.19 (d, J = 5.6); IR 2974, 1763.7, 1431.1, 1372.5, 1248.7, 1208.3, 1083.5, 1001.1; MS; m/e (relative intensity) 182 (M^+ – AcOH 19), 167 (9), 162 (9), 151 (12), 141 (9), 140 (51), 139 (100), 138 (12), 125 (27), 123 (25), 122 (36), 112 (12), 111 (14), 107 (14), 98 (28), 97 (100), 96 (100), 95 (61), 94 (14), 83 (14), 82 (12), 81 (64), 80 (21), 79 (44), 77 (10), 71 (17), 68 (100), 67 (69), 55 (19), 53 (21), 43 (100); HRMS, 182.0968 (M^+ – AcOH), calcd for $C_{10}H_{14}O_3$ 182.0943. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 60.02; H, 6.96.

(2*R*,6*S*)-*trans*-2-(2',2'-Diacetoxyethyl)-6-methyltetrahydropyran (42). The mixture of **41a** and **41b** (60 mg, 0.25 mmol) was hydrogenated in ethanol (5 mL), by using 10% Pt/C (20 mg) under 1 atm of H_2. Upon completion of hydrogen consumption (3 h), the solution was filtered, and the solvent was removed under reduced pressure, affording compound **42** (99%),

which was subjected to hydrolysis without further purification.

42: NMR 6.88 (dd, J = 4.4, 7.2, 1 H), 3.92 (m, H1, H5), 2.25 (ddd, J = 4.4, 9.6, 14.1, 1 H), 2.07 (br s, 6 H, OAc), 1.75 (ddd, J = 4.3, 7.2, 14.1, 1 H), 1.64 (br m, 4 H), 1.27 (br m, 2 H), 1.16 (d, J = 6.4, H6); IR 2926.1, 1766.7, 1433.5, 1375.8, 1250.7, 1204.7, 1127.0, 1058.3, 1013.7; MS (GCMS, CI); m/e (relative intensity) 245, (M + 1, 27), 185 (30), 144 (9), 143 (100).

(2*R*,6*S*)-(*trans*-6-Methyltetrahydropyran-2-yl)acetaldehyde (43). Hydrolysis of **42** was carried out in a freshly prepared solution of sodium methoxide in methanol at room temperature for 5 min, followed by neutralization with methanolic solution of HCl. Solvent was removed under reduced pressure and the residue was extracted with ether to give **43** (60% overall yield from **41**).

43: NMR 9.77 (dd, J = 1.8, 3.3, CHO), 4.38 (m, J = 5.2, 8.7, H1), 3.93 (m, J = 3.3, 6.4, H5), 2.76 (ddd, J = 15.9, 8.7, 3.3, 1 H), 2.45 (ddd, J = 15.9, 5.2, 1.8, 1 H), 1.8–1.5 (m, 4 H), 1.3–1.1 (m, 2 H), 1.18 (d, J = 6.4, H6); IR 2922, 1687.1, 1581.9, 1430.0, 1366.3, 1281.2, 1216.6, 1186.6, 1068.1; MS, m/e (relative intensity) 142 (M^+, 3), 114 (5), 99 (23), 96 (12), 86 (10), 83 (10), 81 (53), 80 (5), 79 (9), 72 (6), 73 (11), 71 (20), 70 (20), 69 (17), 67 (9), 59 (6), 58 (12), 57 (18), 56 (9), 55 (100), 54 (56), 53 (10).

(2*R*,6*S*)-(*trans*-6-Methyltetrahydropyran-2-yl)acetic Acid (44). The aldehyde **43** was oxidized with Jones reagent in acetone to give the corresponding acid **44** in 80% yield. This compound was found to be identical (^{1}H NMR, ^{13}C NMR, IR, MS, optical rotation) with an authentic sample synthesized earlier in these laboratories.[38,42]

Photochlorination of *n*-Alkanes Adsorbed on Pentasil Zeolites

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The photochlorination of *n*-alkanes adsorbed on pentasil zeolites proceeds with up to a 20-fold greater selectivity for the monochlorination of terminal methyl groups compared to the selectivity observed when the reaction is carried out in a homogeneous solution. This enhanced selectivity, which provides a novel means of synthesizing terminally functionalized linear alkanes, was found to be a function of the percent loading of the alkane on the zeolite, the zeolite's silicon to aluminum ratio, the percent conversion of the starting material, and the water content of the zeolite.

Introduction

Recent advances in the chemistry of molecules adsorbed at interfaces are providing organic chemistry with a rich new array of concepts and opportunities that are serving to stimulate innovative approaches to synthetic methodologies and mechanistic investigations.[1,2] Molecular-sieve zeolites represent a novel and unique class of materials which are crystalline, yet porous, which possess enormous internal surface areas, and possess structures and compositions that can be varied over wide ranges.[3] In the case of the *faujasite* zeolites, the Si/Al ratio is routinely varied between 2 and 3 (the X family) and from 3 to 6 (the Y family). In the case of the *pentasil* (ZSM-5 family) zeolites, the subject of this report, the framework composition may be varied over a factor of 20 000 (from a Si/Al ratio of 5 to nearly infinity)! The ZSM-5 zeolites possess exceptionally high stability toward reaction with a variety of reagents and a nearly homogeneous internal surface (i.e., pure SiO_2) with hydrophobic selectivity.[3] Although representing only a small fraction of the tetrahedral atoms making up the framework, the framework aluminum atoms are crucial for the catalytic behavior of these materials.[4] It is reasonable to expect that a variety of unusual properties will accompany the variations in zeolite composition and in zeolite structure.

The ZSM-5 internal surface topology (Figure 1) consists of two types of pore systems (channels), both of which are composed of 10 tetrahedral-membered rings: one is *sinusoidal* with a nearly circular cross section of about 5.5 Å, and the other is *straight* and perpendicular to the sinusoidal channels.[5] The straight channels are roughly elliptical with dimensions of about 5.2 × 5.8 Å.[6]

The LZ-105 type zeolites are also considered to be members of the pentasil families and have been shown to adsorb straight-chain alkanes.[7] It seemed likely to us that the internal topology of the pentasil system would be conducive to reactions that were selective, since *n*-alkanes should be adsorbed within the channels in a manner that might protect the backbone CH_2 groups from attack by reactive diffusing reagents such as chlorine atoms. In an overly simplistic view, the terminal methyl hydrogens, which are less reactive toward chlorine atoms than the secondary hydrogen in solution chlorination, might become more reactive because of the restrictions on diffusion of the chlorine atoms into the channels where they would

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