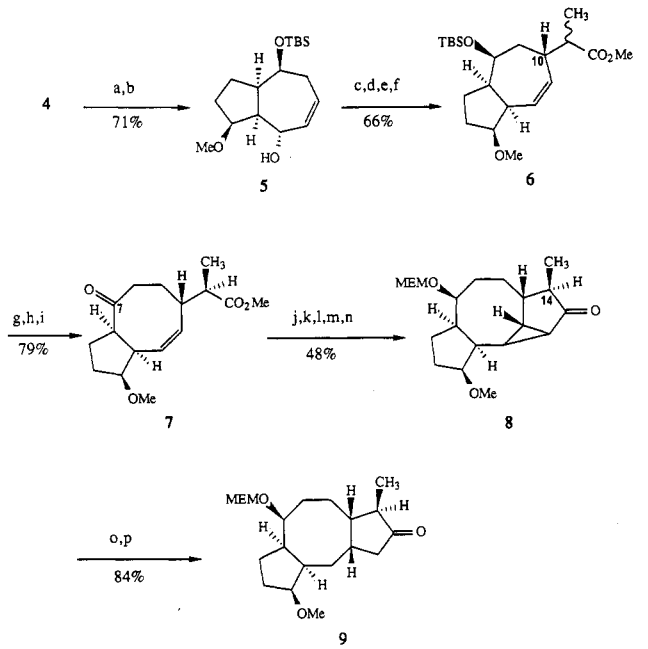
Scheme I[a]



[a] (a) *m*-CPBA, −78 °C; (b) $(MeO)_3P$, 65 °C; (c) $(C_2H_5CO)_2O$, Et_3N, DMAP; (d) LDA, TBDMSCl, −78 °C; (e) 110 °C, MePh; (f) CH_2N_2, Et_2O; (g) Bu_4NF, room temperature; (h) $(COCl)_2$, DMSO, Et_3N, −78 °C; (i) $TMSCHN_2$, $BF_3{\cdot}Et_2O$, −40 °C; (j) $NaBH_4$, 0 °C; (k) MEMCl, Et_2-*i*-PrN; (l) LiSPr, HMPA, room temperature; (m) $(COCl)_2$/collidine; (n) CH_2N_2, $Cu/CuSO_4/C_6H_{12}$/reflux; (o) Li/NH_3; (p) PDC.

fluxing toluene for several hours provided the rearranged product **6** as an easily separable 85:15 mixture of epimers at the side-chain methyl substituent in 66% overall yield. This mixture was isolated as the methyl esters (CH_2N_2, Et_2O). The major isomer was separated and carried through the remainder of the synthesis. Removal of the TBDMS group from the C_{10} alcohol and Swern oxidation[10] gave the corresponding cycloheptanone in 90% yield. Exposure of this ketone to (trimethylsilyl)diazomethane in the presence of $BF_3{\cdot}Et_2O$ at −40 °C[11] resulted in a smooth, regiospecific one-carbon ring expansion to the cyclooctanone **7** (mp 57–58 °C; C=O ν_{max} 1710 cm^{-1}) in 88% yield. Interestingly, none of the regioisomeric ketone was detected in this reaction. This observation is consistent with previous results in which the sterically less congested carbon migrates preferentially.

At this crucial juncture in the synthetic scheme, a single-crystal X-ray structure was obtained on compound **7**, which verified the direction of the ring expansion and, more importantly, established the relative stereochemistry of the vicinal protons at the side chain as being correct for ceroplasteric acid (**1**).

The stage was now set to complete the construction of the 5-8-5 tricycle with the required relative stereochemistries at C_6, C_{10}, and C_{14}. The C_7 ketone in compound **7** was reduced with $NaBH_4$ at 0 °C to give a 94% yield of a single alcohol, which was presumed to be the β-configuration based on examination of molecular models. The resultant hydroxyl group was then protected as the MEM ether. Next, the methyl ester was cleaved to the corresponding carboxylic acid via a mild S_n2-type dealkylation procedure employing excess lithium thiopropoxide in HMPA at room temperature.[12] This method for obtaining the acid from the ester was deemed prudent at this stage of the synthesis in order to minimize the risk of epimerization at the side-chain methyl substituent. Routine conversion into the diazo ketone via the corresponding acid chloride and copper-mediated insertion[13] into the cyclooctene double bond gave the desired cyclopropyl ketone **8** as a single isomer in 48% yield for the six steps. Reductive cleavage of the cyclopropane bond which was best aligned with the C_{13} carbonyl group under dissolving metal conditions (Li/NH_3)[14] followed to give, after PDC oxidation, the tricyclic ketone **9** (C=O ν_{max} 1744 cm^{-1}) in 84% yield.[15]

Ketone **9** possesses most of the key structural features of the hydrodicyclopenta[*a*,*d*]cyclooctane ring system as well as displaying the correct stereochemical arrangements at several important positions. Work is now under way to utilize this strategy in the total synthesis of ceroplasteric acid and related natural products.

Acknowledgment. This research was funded by the National Institutes of Health through grant GM-30771. We thank Paul Kierkus for obtaining the X-ray structure of compound **7**.

Supplementary Material Available: Spectral and analytical data for compounds **3–9** and fractional coordinates and temperature parameters, bond distances, and angles for **7** (3 pages). Ordering information is given on any current masthead page.

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(15) The identity of all new compounds reported in this paper was established by IR, ^1H NMR, ^{13}C NMR, and MS. The elemental compositions were determined by combustion analysis or HRMS.

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A New Method for the Synthesis of O-Glycosides from S-Glycosides

Summary: Treatment of S-glycosides with $NOBF_4$ produced highly reactive glycosyl donors which in the presence of glycosyl acceptors gave O-glycosides in high yields.

Sir: Stereospecific construction of O-glycosidic linkages is of paramount importance in natural product chemistry.[1] One of the problems involved is the generation, from stable precursors, of a reactive glycosylating species[2] which can form a covalent bond with the glycosyl acceptor in a stereospecific fashion. Disadvantages of glycosyl halides, which are still the most frequently used glycosyl donors, have been well-documented.[2b] 1-O-Acetates of mono- and

(1) For some recent examples, see: (a) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466 and references cited therein. (b) Katano, K.; Millar, A.; Pozsgay, V.; Primeau, J. L.; Hecht, S. M. *J. Org. Chem.* **1986**, *51*, 2927. (c) Roush, W. R.; Straub, J. A. *Tetrahedron Lett.* **1986**, *27*, 3349.
(2) For recent reviews, see: (a) Paulsen, H. *Angew. Chem.* **1982**, *94*, 184; *Angew, Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

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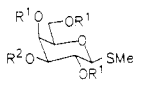
Table I. Synthesis of O-Glycosydes from S-Glycosydes by Activation with $NOBF_4$[a]

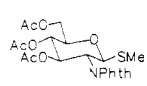
entry	glycosyl donor	glycosyl acceptor	product[b]	isolated yield (%)
1	1	9	13	67
2	1	10	14	74
3	3	11	15	90
4	4	12	16	72
5	2	11	17[c]	74
6	4	11	18	81
7	5	11	18	75
8	6	11	18	73
9	7	11	19	68
10	8	11	19	75

[a] Typically, a mixture of 0.55 mM of donor, 0.5 mM of acceptor, 0.5–1 g of powdered, 4-Å molecular sieves, and 5 mL of anhydrous methylene chloride was stirred at 0–25 °C under dry nitrogen for 30 min before addition of $NOBF_4$ (0.55 mM). The course of reaction was followed by TLC. After disappearance of the starting compounds the product was isolated by extractive and chromatographic workup. [b] Satisfactory elemental analytical data have been obtained for all products reported. Selected ^{13}C NMR spectroscopic data (50 MHz, $CDCl_3$) δ **13** 101.2 (C-1', $J_{C\text{-}1',H\text{-}1'}$ = 159 Hz), 102.8 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 160); **14** 101.5 (C-1', $J_{C\text{-}1',H\text{-}1'}$ = 169), 104.9 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 162); **15** 97.7 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 166), 99.4 (C-1', $J_{C\text{-}1',H\text{-}1'}$ = 166); **16** 99.1 (C-1'), 99.7 (C-1); **17** 97.9 (C-1), 101.8 (C-1'); **18** 97.8 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 169), 98.5 (C-1', $J_{C\text{-}1',H\text{-}1'}$ = 170); **19** 95.7 (C-1', $J_{C\text{-}1',H\text{-}1'}$ = 174), 97.8 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 167); **20** 95.5 (C-1', $J_{C\text{-}1',H\text{-}1'}$ = 172), 97.9 (C-1, $J_{C\text{-}1,H\text{-}1}$ = 167). [c] Isolated as a ca. 2:3 mixture of the 1,2-trans and 1,2-cis anomers.

oligosaccharides, under catalysis by trimethylsilyl trifluoromethanesulfonate,[3] seem to be superior in individual cases but the extremely strong acid generated during the reaction limits the scope of this approach. Recently, stable



1 R^1=R^2=Ac
2 R^1=Bn, R^2=Ac



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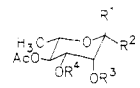
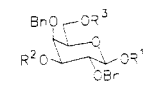
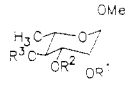


4 R^1=SMe, R^2=H, R^3=R^4=Ac
5 R^1=H, R^2=SMe, R^3=R^4=Ac
6 R^1=SPh, R^2=H, R^3=R^4=Ac
7 R^1=SMe, R^2=H, R^3,R^4=CMe_2
8 R^1=H, R^2=SMe, R^3,R^4=CMe_2



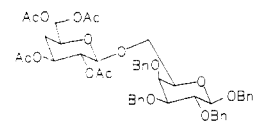
9 R^1=R^2=Bn, R^3=H
10 R^1=Me, R^2=H, R^3=Bn



11 R^1,R^2=CMe_2, R^3=H
12 R^1=H, R^2=R^3=Bn

S-glycosides, which can be prepared by a number of procedures,[4] have found increasing use as glycosyl donors. The basis for this is the nucleophilicity of the bivalent sulfur atom to electrophilic reagents such as NBS,[4e] methyl trifluoromethanesulfonate,[5] and dimethyl(methylthio)-sulfonium trifluoromethanesulfonate[6] which generate from S-glycosides an unstable sulfonium species that reacts with the nucleophilic aglycon.[7] Deficiencies in the above approaches, which include reported low yields, long reaction times, and high toxicity of the reagents which is further aggravated by difficulties in their handling, necessitate[8] further research in this area. We now report our discovery of a new activation of S-glycosides that is a mild, fast, and high-yielding method to construct O-glycosidic linkages.

Specifically, it was found that the readily available methyl S-glycosides[4g] can be activated under anhydrous conditions with an equimolar amount of nitrosyl tetrafluoroborate[9] in methylene chloride at temperatures between 0 and 25 °C to give, in the presence of a hydroxylic component (in equimolar or nearly equimolar amount) high yields of O-glycosides (Table I) in short reaction times (30 min–3 h). Primary and secondary hydroxyl groups can be glycosylated equally well and the procedure can be used also to successfully glycosylate relatively unreactive hydroxyls (entry 4). The original stereochemistry of the S-glycosidic linkage is not crucial to either the stereochemical outcome or final yield of this glycosylation reaction (entries 6 and 7). Furthermore, phenyl S-glycosides, which are equally readily available,[4e] can also be used as demonstrated by entry 8, which further widens the applicability of this methodology. Acid-sensitive protecting groups such as O-isopropylidene or O-benzyl groups are compatible with the reaction conditions. The stereochemical result of the new glycosylation reaction is primarily determined by the properties of the group at C-2: a participating group[2a] such as acetoxy (entries 1, 2, 4, 7, and 8) or *N*,*N*-phthaloylamino group (entry 3) favors the exclusive formation of a 1,2-trans-O-glycosidic linkage. On



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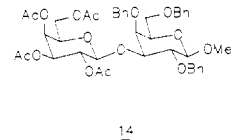

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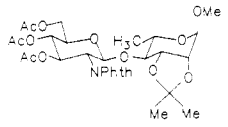

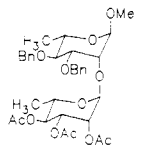

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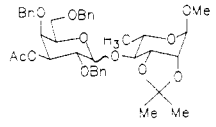

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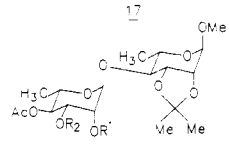

17

18 R^1=R^2=Ac
19 R^1,R^2=CMe_2

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(9) For the use of NO_2BF_4 to initiate the transformation of dithioacetals to the corresponding carbonyl compounds, see: Olah, G. A.; Narang, S. C.; Salem, G. F.; Gupta, B. G. B. *Synthesis* **1979**, 273.

the other hand, a nonparticipating group[2a] at C-2 has no directing effect on the final stereochemistry at C-1 that is determined by an interplay of additional factors as exemplified by entries 5, 9, and 10.

Mechanistically, the new glycosylation reaction is thought to proceed by the intermediate formation of an S-nitrosyl species which generates a reactive glycosyl cation that in the presence of a participating group at C-2 could get further stabilization by the formation of a dioxocarbenium cation.[2a] Finally, the reaction is completed by nucleophilic attack of the glycosyl acceptor at C-1.

The present methodology should contribute to the construction of O-glycosidic linkages in carbohydrate-containing, complex natural products. The scope of this approach, including the possible use of other potential nitrosyl donors, is under investigation in our laboratory.

Registry No. 1, 55722-48-0; 2, 110224-77-6; 3, 79528-48-6; 4, 84635-55-2; 5, 110224-78-7; 6, 108740-74-5; 7, 110224-79-8; 8, 110224-80-1; 9, 35017-04-0; 10, 55697-53-5; 11, 14133-63-2; 12, 69558-07-2; 13, 110224-81-2; 14, 110224-82-3; 15, 110224-83-4; 16, 71348-34-0; α-17, 110224-84-5; β-17, 110224-86-7; 18, 53130-93-1; 19, 110224-85-6; $NOBF_4$, 14635-75-7.

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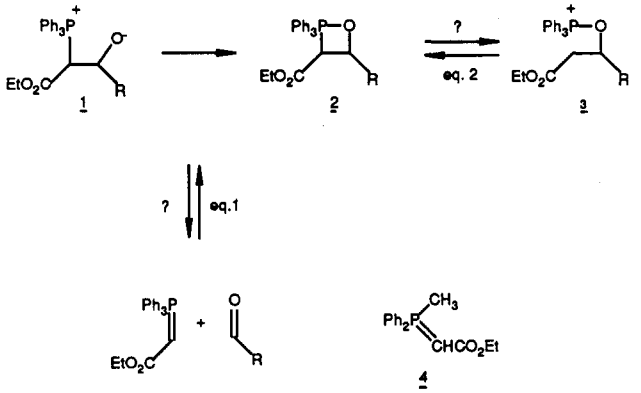
Evidence against Reversible Wittig Reaction of a Stabilized Ylide: High (*E*)-Olefin Selectivity under Kinetic Control

Summary: The betaine **10**, generated by deprotonation from deuterium-labeled **8**-*d*, decomposes stereospecifically to the (*Z*)-alkene. The corresponding Wittig reaction of ylide **4** with cyclohexanecarboxaldehyde, which gives a 95:5 (*E*)-/(*Z*)-alkene ratio, therefore occurs under kinetic control, without equilibration or Wittig reversal.

Sir: High (*E*)-olefin selectivity of carbonyl-stabilized phosphonium ylide + aldehyde reactions has been attributed to reversible formation of betaines (eq 1).[1] This

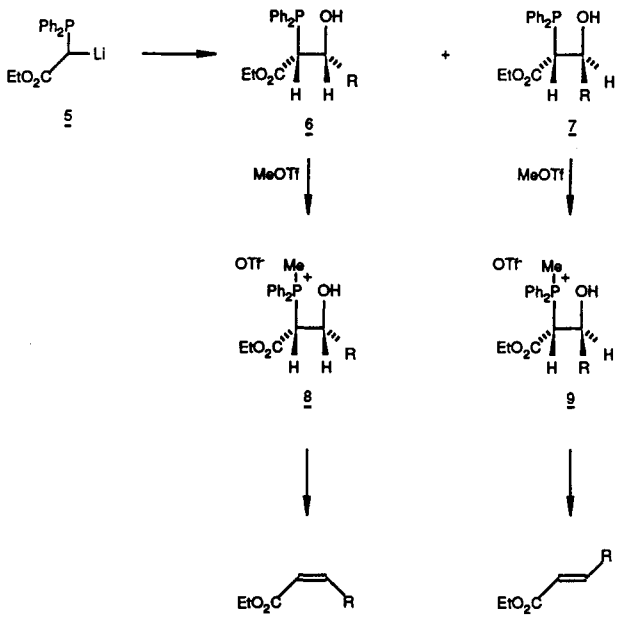


scheme has become widely accepted even though authors of the original control experiments (ethyl phenylglycidate + triphenylphosphine, refluxing ethanol, gives cinnamate with partial loss of stereochemistry) were careful not to make broad generalizations. Speziale and Bissing demonstrated *partial* reversal of intermediates using crossover experiments, but they recognized that interpretation of the results was difficult due to isomerization of product geometry and the possible intervention of other reaction pathways.[2] More recently, it has become clear that oxaphosphetanes **2** are much more stable than betaines **1**,[3] and an additional pathway for stereochemical equilibration has been suggested via the reversible formation of **3** from **2** (eq 2).[4] If either pathway (eq 1 or eq 2) is involved, then preferential decomposition of the trans-disubstituted oxaphosphetane would presumably explain the high (*E*)-olefin selectivity.

Our suspicions regarding the retro-Wittig rationale were aroused by a variety of considerations. For example, experiments in our laboratory had shown that oxaphosphetanes derived from *moderated* ylides are too short-lived at −70 °C for NMR detection or acid quenching experiments.[5] Could **2** be more resistant to olefin formation, sufficiently so for equilibration to compete? Furthermore, cis-disubstituted oxaphosphetanes corresponding to *nonstabilized ylides* decompose faster than do the trans isomers.[6] Could **2** be so different in terms of relative rates for (*E*)- vs (*Z*)-olefin formation? Since **2** cannot be detected due to its short lifetime, we have used the method of indirect oxaphosphetane formation to probe the intermediates corresponding to the stabilized ylide **4**.

As shown in Scheme I, addition of lithio phosphine **5**[8] to cyclohexanecarboxaldehyde gave a mixture of phosphines **6** and **7** (ca. 3:1 ratio[9]). The phosphines proved

Scheme I



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