organo ylides offer a challenging synthetic goal. Theoretical calculations on hypervalent iodine structures are possible and should yield important information about bonding.

I believe that in the future hypervalent iodine will assume a role in organic chemistry of comparable importance to boron, silicon, sulfur, selenium, and phosphorus.

We thank the Petroleum Research Fund PRF-14773-AC1 for support of this work.

Registry No. Iodine, 7553-56-2.

Hetero-Diels–Alder Reaction in Highly Functionalized Natural Product Synthesis†,[1]

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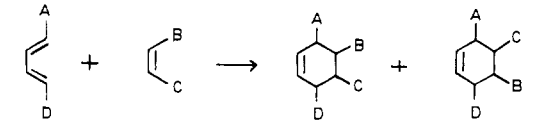
Functionally substituted dihydro- and tetrahydrofuran and -pyran structures play an important role as intermediates in syntheses of highly functionalized natural products. They are not only present in carbohydrates and related natural products, but they are also useful as chiral precursors in the synthesis of various classes of naturally occurring compounds.[2] The "chiron approach"[3] to such intermediates from carbohydrates is often lengthy and tedious because of multiple regiospecific and stereocontrolled functional group manipulations. Therefore de novo syntheses from achiral starting materials have become competitive or even superior.[4-9] Due to the nature of the target molecules a suitable method could be based on the Diels–Alder approach.[8,9]

The Diels–Alder reaction has become a powerful tool in natural product synthesis because it combines C–C bond formation with regio- and diastereoselectivity at several centers.[10] Due to supra–suprafacial reaction, polarity controlled orientation, and endo/exo selectivity of diene and dienophile, very often only one pair of enantiomers is obtained out of the maximum 32 possible isomers (Scheme I, the total number of possible isomers is reduced by each specificity by a factor of two). In addition, intramolecularity has been used extensively in support of this selectivity.[11] This selectivity can be explained in terms of frontier orbital overlap, which also differentiates the normal and inverse type Diels–Alder reaction and thus verifies the observed reactivity pattern of different diene/dienophile combinations.[12,13] Recently even enantioselectivity could be introduced successfully into the Diels–Alder reaction, leading to preferential or exclusive formation of one single stereoisomer.[14]

The incorporation of functional groups, especially electron-donating heterosubstituents, in the Diels–Alder adducts is most conveniently achieved by reactions with the corresponding electron-rich 1,3-dienes and dienophiles, respectively. The 1- and 2-monohetero- and the 1,3-diheterosubstituted 1,3-dienes have been extensively

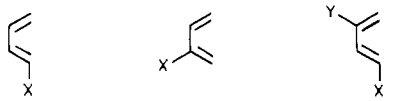
Scheme I



2^4 Stereoisomers 2^4 Stereoisomers

Nonspecific Cycloaddition	⟶	$2^1 \times 2^4 = 32$ Isomers
+ Supra-suprafacial Specificity	⟶	$2^1 \times 2^2 = 8$ Isomers
+ Regiospecificity	⟶	$2^0 \times 2^2 = 4$ Stereoisomers
+ Endo/exo-Specificity	⟶	$2^0 \times 2^1 = 2$ Stereoisomers (Racemate)
+ Enantiospecificity	⟶	$2^0 \times 2^0 = 1$ Stereoisomer

Scheme II[a]



X = OR	X = OR	X = OMe, Y = $OSiMe_3$
X = SR	X = SR	X,Y = NR_2
X = NR_2	X = NR_2	
X = N-COOR H		R = Alkyl, Acyl, $SiMe_3$

[a] References 4–7 and 10.

† This Account is dedicated to the memory of Wolfgang Abele, who contributed so much to this work.

(1) De novo Sythesis of Carbohydrates and Related Natural Products, Part 21. Part 20: Küfner, U.; Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 90; *Angew. Chem., Inst. Ed. Engl.* **1986**, *25*, 89.
(2) Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, 1983.
(3) "Chiron Approach" is the transformation of easily available chiral templates into enantiomerically pure chiral synthons; see ref 2.
(4) Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 1.
(5) Hoppe, D. *Nachr. Chem., Techn. Lab.* **1982**, *30*, 403.
(6) McGarvey, G. J.; Kimura, M; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.
(7) Danishefsky, S.; Webb, R. R., II *J. Org. Chem.* **1984**, *49*, 1955, and references therein.
(8) Schmidt, R. R.; Angerbauer, R. *Angew. Chem.* **1977**, *89*, 822; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 783.
(9) Schmidt, R. R.; Maier, M. *Tetrahedron Lett.* **1985**, *26*, 2065, and references therein.
(10) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, *753*, and references therein.
(11) Oppolzer, W. *Angew. Chem.* **1977**, *89*, 10; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. Ingendoh, A. *Pharm.* **1982**, *11*, 48. Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.

Richard R. Schmidt received his Ph.D. from Stuttgart University working with Professor R. Gompper. After postdoctoral work with Professor Frank M. Huenneckens at Scripps Clinic, La Jolla (1965–1966), he became a Privat dozent at Stuttgart University 1969. In 1975 he was appointed professor of chemistry at Konstanz University. His current research interests are in glycoconjugate synthesis, cycloaddition reactions, and reactions with highly functionalized vinyllithium compounds for natural product syntheses.

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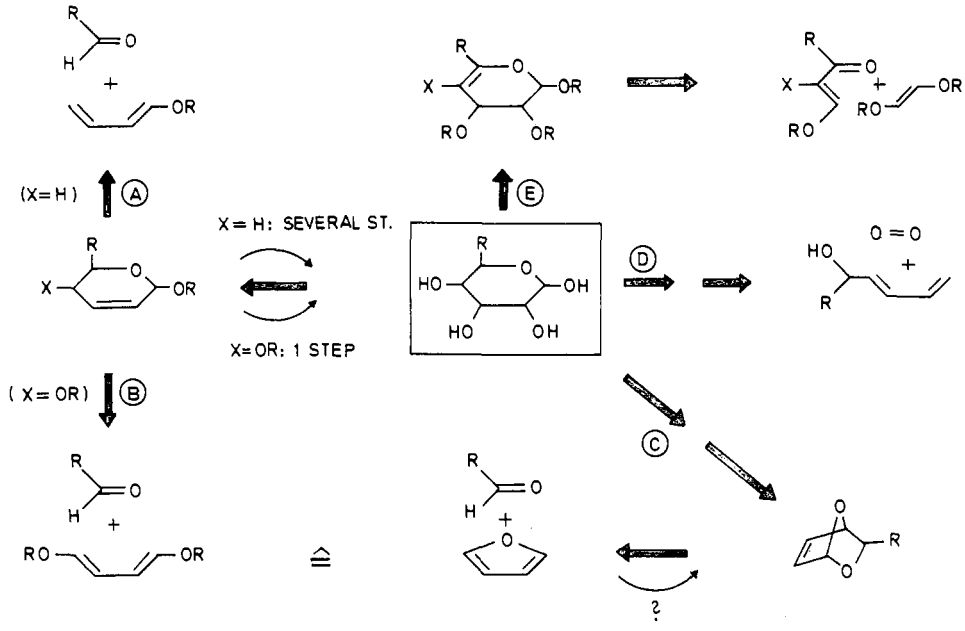
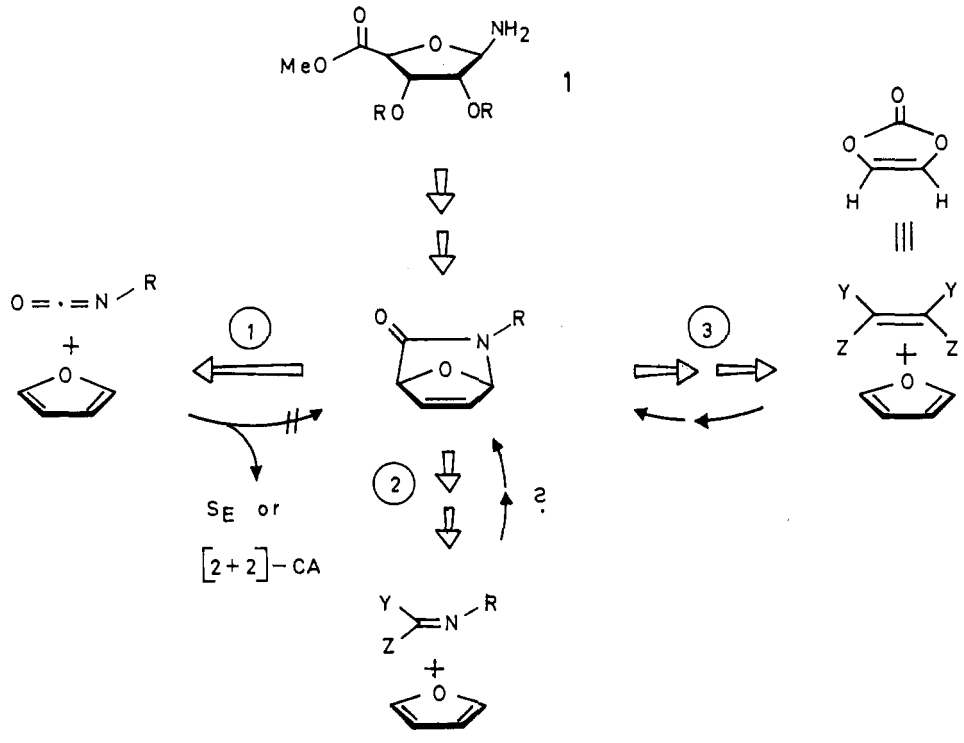
Scheme III



Scheme IV



studied in Diels–Alder reactions (for instance, the 1,3-diene types in Scheme II).[4–7,10,15,16] They have served as versatile starting materials in various natural product and some carbohydrate related syntheses (see Scheme III, route A) as exemplified by Zamojski's and by David's work with 1-oxy-1,3-dienes and by Danishefsky's work with 1,3-dioxy-1,3-dienes and derivatives, extensively considered in recent reviews.[4–6,10,15,16]

We have been mainly concerned with short syntheses of carbohydrates and related highly functionalized natural products possessing hetero substituents not only in the 1-, 2-, or 1,3-positions, but also in the 4-position of the 1,3-diene derived portion.[8,17] Therefore we have extensively investigated direct 1,4-functional group introduction via normal type Diels-Alder and hetero-Diels–Alder reactions, leaving the incipient CC-double bond for convenient subsequent functionalization at the C-2 and/or C-3 position[8,17] (Scheme III, routes B–D). In addition, inverse type hetero-Diels–Alder reactions between functionally substituted 1-oxa-1,3-dienes and electron-rich dienophiles have been probed for this

(12) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.
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(15) Blechert, S. *Nachr. Chem. Tech. Lab.* **1980**, *28*, 167.
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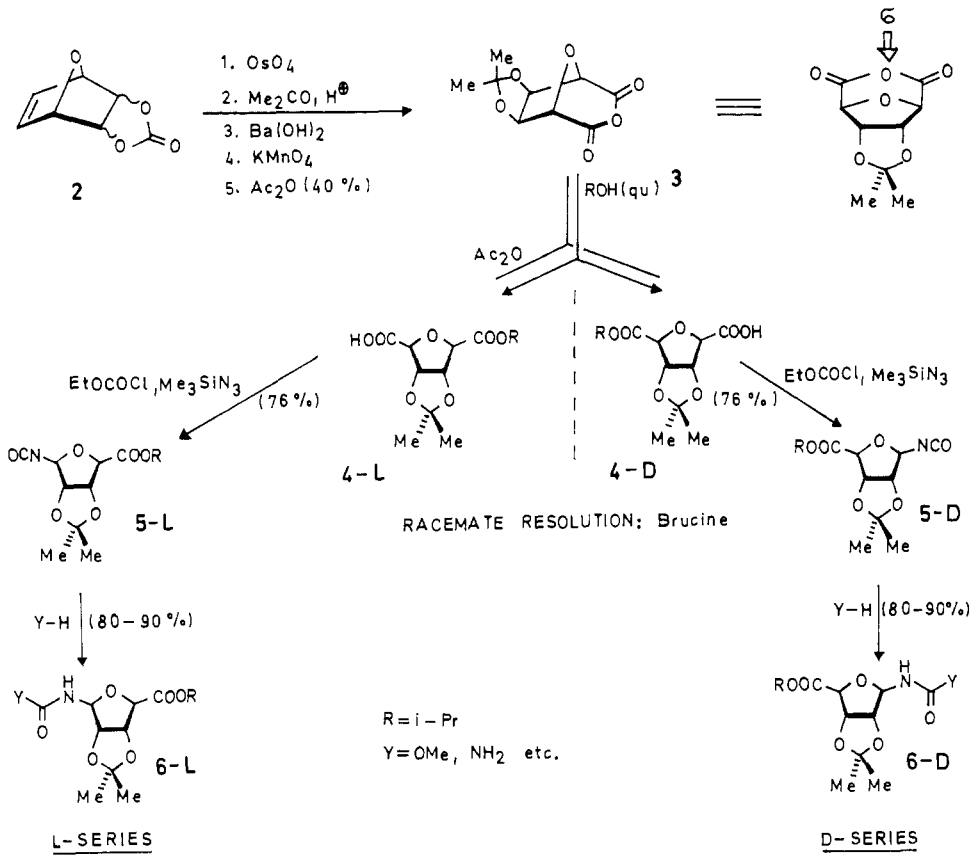
(17) Forrest, A. K.; Schmidt, R. R. *Tetrahedron Lett.* **1984**, *25*, 1769, and references therein.

Scheme V



purpose[9] (Scheme III, route E). Most importantly, eliminative loss of functional groups during these operations had to be avoided.

Furan as 1,4-Diheterosubstituted Electron-Rich 1,3-Diene

Demonstration of the versatility of the Diels–Alder approach in carbohydrate synthesis came from attempts to synthesize nucleoside uronates **1** (Scheme IV), which were required for the formation of 5′,5″-dideuterated nucleosides in coenzyme B_{12} enzymatic studies[18] and because of the uronates' interesting physiological properties.[19] Direct oxidation of available nucleosides and glycosidic bond formation between ribofuranuronates and the required heterocycles provoked many difficulties.[18,19]

According to route C in Scheme III, a Diels–Alder approach was envisaged with furan as the 1,4-disubstituted electron-rich 1,3-diene (Scheme IV). However, hetero-Diels–Alder reaction with isocyanate (route 1) was not viable because [2 + 2]-cycloaddition or electrophilic substitution predominate with this reagent; the same result was obtained for other CN multiple bond systems for instance, electron-poor imines or tosylcyanide which are often sucessfully applied in [2 + 4]-cycloaddition reactions (route 2).[20] Therefore the required nitrogen atom was replaced by carbon (route 3). In this strategy the disadvantage of having the wrong element was compensated for by gaining a meso-type compound, which could lead to enantioselectivity via the meso trick.[20]

To this end vinylene carbonate adduct **2**[21] (Scheme V) was transferred via exo-specific dihydroxylation, protection and deprotection steps, oxidative *cis*-diol cleavage, and acetic anhydride treatment into *meso*-anhydride **3** containing the required relative stereochemistry. Reaction with isopropanol, racemate resolution into **4**-D and **4**-L, reconversion of the undesired isomer into *meso*-anhydride **3**, and Curtius degradation of the wanted isomer afforded the β-isocyanate of either D- or L-ribofuranuronate (**5**-D or **5**-L) required in nucleoside uronate synthesis.[20,22] The same method was also successfully applied to the synthesis of the corresponding D- or L-*lyxo* compounds.[23] A variety of enantiospecific carbohydrate syntheses may be designed on *meso*-7-oxanorbornenes analogous to compound **2** as intermediates. Most importantly, loss of the meso structure has to be carried out in a conveniently reversible step.[24]

7-Oxa-2-norbornanones were intermediates in the synthesis of the corresponding *ribo*-hexofuranuronates.[25]

(18) Schmidt, R. R. *Angew. Chem.* **1967**, *79*, 1017; *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 997. Schmidt, R. R.; Schloz, U.; Schwille, D. *Chem. Ber.* **1968**, *101*, 590. Babior, B. M. *Acc. Chem. Res.* **1975**, *8*, 376. Abeles, R. H.; Dolphin, D. *Acc. Chem. Res.* **1976**, *9*, 114.

(19) Jung, K.-H.; Schmidt, R. R. *Chem. Ber.* **1980**, *113*, 1775, and references therein.

(20) Lieberknecht, A. Dissertation, Universität Stuttgart, 1978.

(21) This compound was obtained as described: Newman, M. S.; Adder, R. W. *J. Am. Chem. Soc.* **1959**, *77*, 3789; *Ibid.* **1966**, *88*, 3885.

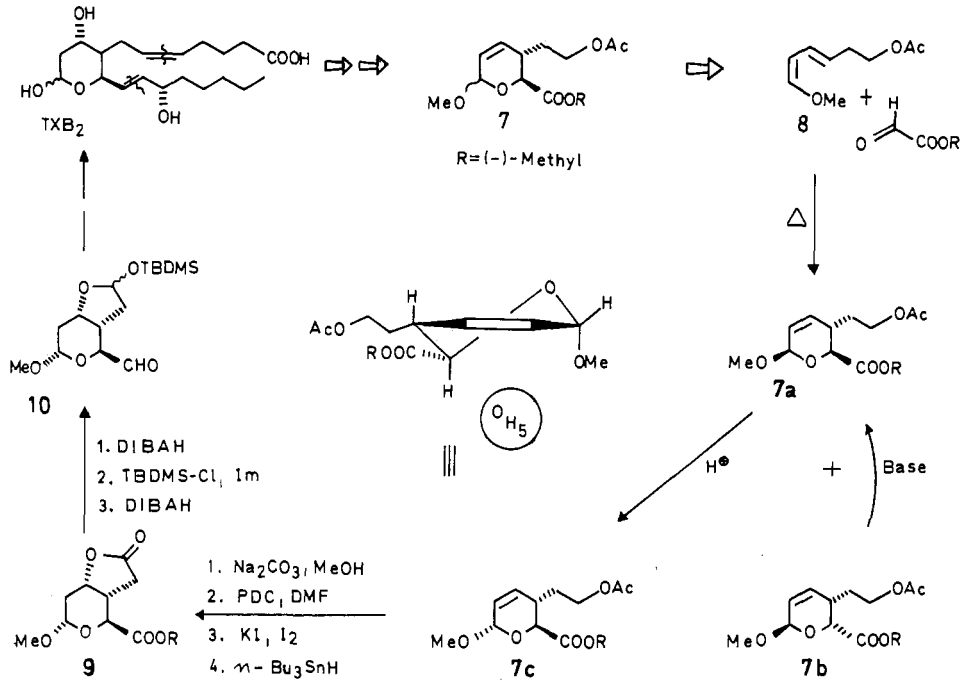
(22) Schmidt, R. R.; Lieberknecht, A. *Angew. Chem.* **1978**, *90*, 821; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 783.

(23) Beitzke, Ch. Dissertation, Universität Konstanz, 1982.

(24) 7-Oxanorbornene derivatives were quite often used as intermediates in the synthesis of racemic carbohydrates and related compounds.[4] However, the conveniency of intermediate meso compounds to gain enantioselectivity was only recently considered in the synthesis design: Ohno, M.; Ito, Y.; Arita, M.; Shibata, T.; Adachi, K.; Sawai, H. *Tetrahedron* **1984**, *40*, 145.

(25) Schmidt, R. R.; Beitzke, Ch.; Forrest, A. K. *J. Chem. Soc., Chem. Commun.* **1982**, 909, and references therein. For a recent reference, see: Warm, A.; Vogel, P. *Tetrahedron Lett.* **1985**, *26*, 5127.

Scheme VI



1,4-Functionally Substituted 1,3-Butadienes as Furan and Pyrrole Equivalents

For furan to be a generally useful precursor for furanose and pyranose syntheses, [2 + 4]-cycloadditions with various aldehydes would be required (Scheme III, route C). However, this reaction has not been realized yet; this is also true for other interesting precursors, for instance pyrrole and thiophene.[26] Therefore it was looked for synthetic equivalents possessing higher reactivity towards aldehydes. Earlier work mainly by Zamojski[4] indicated that O-protected 1-oxy-1,3-butadienes react readily with glycoxylates and mesoxalates (Scheme III, route A).[4,27,28] Under high pressure even nonactivated aldehydes have recently been used as dienophiles.[29,30] Because of stronger electron polarization, 1,3-dioxy-substituted 1,3-butadienes (the Danishefsky dienes) were particularly reactive. Under acid catalysis even reaction with normal aldehydes was observed[16,31] and with chiral lanthanide complexes as mild acid catalysts enantioselectivity could be induced successfully.[32]

This methodology is not only of interest for the synthesis of 4-deoxy sugars[4] but also for branched and especially C-4 branched sugars.[30] We have exemplified this for the thromboxane B_2 (TXB_2) synthesis analyzed in Scheme VI:[30] Disconnection of the side chains at the double bonds and elimination of water leads to dihydropyran 7 which should be readily available from glyoxylate and the electron-rich 1,3-diene 8 having the required functional C_2-substituent in 4-position. When this reaction was attempted, no diastereoselection was observed; it afforded the branched pseudoglycals **7a,b** in a 1:1-ratio. However, base treatment of stereoisomer **7b** furnished the theromodynamically more favorable stereoisomer **7a** with both carbon substituents on different sites of the molecule, and acid treatment converted this material into stereoisomer **7c** due to the anomeric and allylic effects favoring the $^0H_5$-conformation. Both these stereoelectronic effects have a big impact on the conformation and configuration of acetal and allyl alcohol systems, respectively.[33] In compound **7c**, with the desired relative stereochemistry of the carbon substituents, the required hydroxy group was introduced diastereospecifically via intramolecular lactonization following Corey's procedure.[34] The lactone **9** thus obtained was subsequently transferred into the partially protected trialdehyde **10** required for thromboxane B_2 formation by selective reduction of the lactone and the ester moiety with diisobutyl aluminum hydride (DIBAH) at different temperatures.

For straightforward syntheses of hexopyranoses we became interested in hetero-Diels–Alder reactions of 1,4-dioxysubstituted 1,3-butadienes and carbonyl compounds (Scheme III, route B).[8] This would avoid any additional functionalization of the 2-, 4-, or 2- to 4-positions required partly due to eliminative loss of functional groups during cycloaddition with 1,3-dioxy substituted and with tri- or tetraoxy substituted dienes;[7,16,31] this problem could be partly prevented now by mild acid catalysis.[31,32] Because the mesomeric effects of the 1,4-dioxysubstituents in 1,3-butadienes are opposed, a dramatic lowering in reactivity compared with the systems in Scheme III was expected; this could be partially relieved by using electron withdrawing acyl groups for protection of the oxygen atoms. Therefore we investigated the hetero-Diels–Alder reaction of *trans,trans*-1,4-diacetoxy-1,3-butadiene (**11**)[35] as the

(26) Wagner-Jauregg, T. *Synthesis* **1980**, 165.
(27) Mieczkowski, J.; Zamojski, A. *Carbohydr. Res.* **1977**, *55*, 177, and references therein.
(28) Schmidt, R. R.; Vogt, K. *Synthesis* **1983**, 799.
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(31) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761. Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.* **1985**, *107*, 7762, and references therein.
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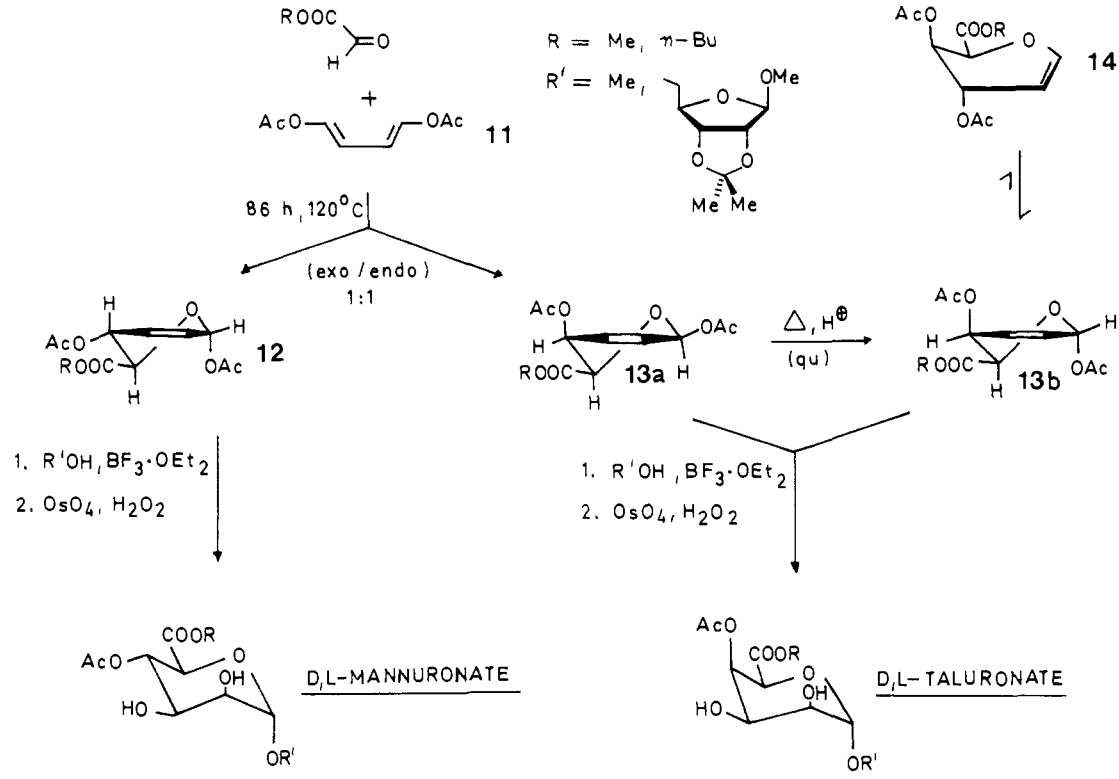
(33) Angerbauer, R.; Schmidt, R. R. *Carbohydr. Res.* **1981**, *89*, 19.
(34) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.

Scheme VII



furan equivalent (Scheme VII) with various carbonyl compounds as heterodienophiles. We were able to find conditions for the reaction with activated carbonyl compounds, yielding, for instance, with glyoxylates the pseudoglycals **12** and **13a**.[8]

We gained further insight into the operation of the allylic and anomeric effects, which strongly influence the preferred conformation in pseudoglycals with a 4-acyloxy substituent and thus the relative stereochemistry of the product. This resulted, for instance, in complete transformation of compound **13a** into stereoisomer **13b** with the $^0H_5$-conformation, having both acetoxy substituents in pseudoaxial position.[33,36] In addition, compound **13b** is in equilibrium with a small amount of glycal **14** via a [3.3]-sigmatropic rearrangement of the 1-acetoxy substituent. This leads to useful stereocontrol of three adjacent chiral centers through a simple cycloaddition reaction and a subsequent glycal specific reaction. However, the most interesting and thus far unprecedented observation was the high reactivity of 1-acyloxy-substituted pseudoglycals in O- and N-glycosidation reactions. The 1-acetoxy substituent in compounds **12** or **13a,b** was replaced upon mild acid catalysis by various glycosyl acceptors (Scheme VII) to give the corresponding α-glycosides. Cis-dihydroxylation of these compounds with osmium tetroxide/hydrogen peroxide took place exclusively from the β-site providing D,L-mannuronate and D,L-taluronate, respectively. Thus the efficiency of 1,4-diacetoxy butadiene based approaches to dihydropyran and pyranoses were exhibited.[36]

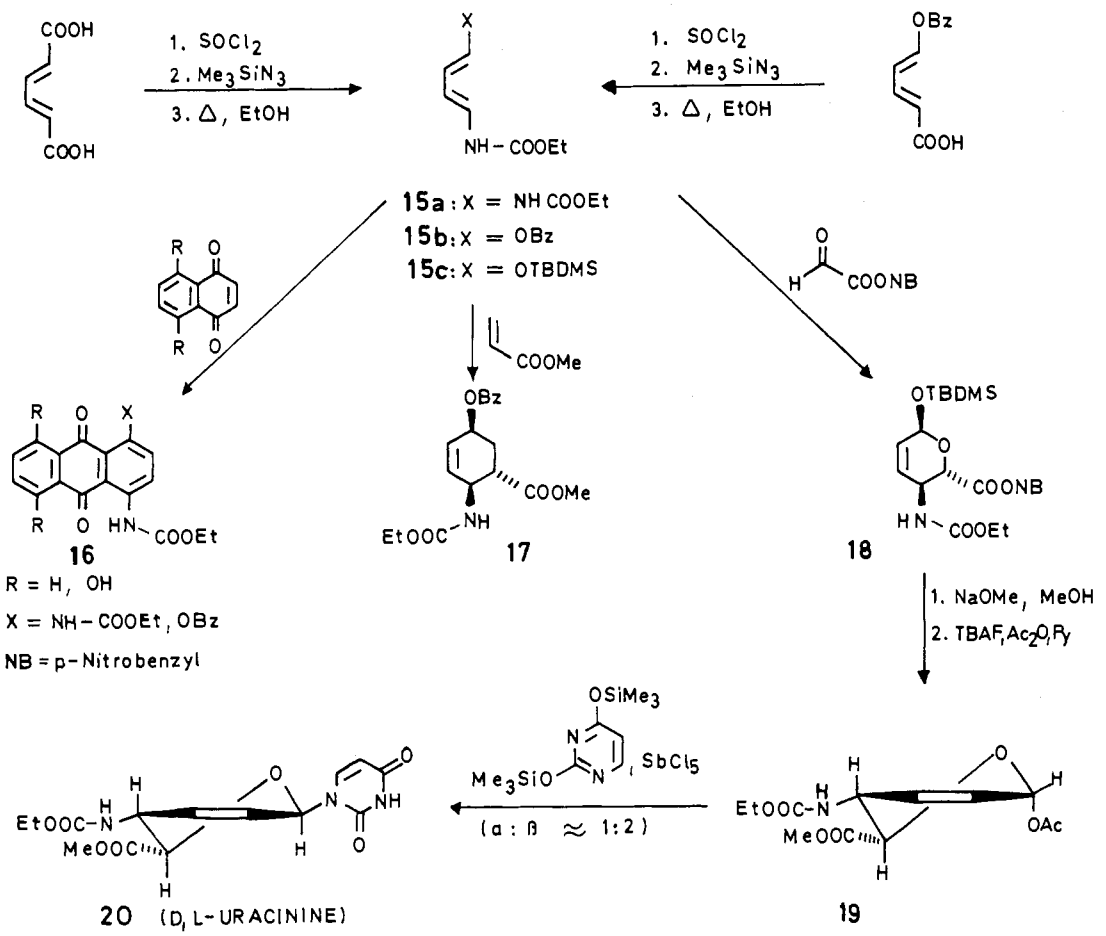
The usefulness of 1,4-diacetoxybutadiene **11** in Diels–Alder reactions with CC-dienophiles for the synthesis of highly functionalized natural products has largely been ignored in current literature on heterosubstituted 1,3-dienes.[10] We added the reaction with benzyne, giving convenient access to *cis,cis*-naphthalene dioxide and to the corresponding epoxidol.[37]

N-acylated 1,4-diaminobutadiene **15a**, being a pyrrole synthon, is readily obtained from muconic acid via Curtius degradation (Scheme VIII).[38,39] This compound proved to be an interesting 1,3-diene for reactions with C–C dienophiles as indicated by the formation of compounds **16** (Scheme VIII). However, compared to 1,4-diacetoxybutadiene **11**, it exhibited much lower reactivity in hetero-Diels–Alder reactions. In addition, the high reactivity of the corresponding pseudoglycals in glycosidation reactions was lost, due to the lower leaving group character of the (ethyloxycarbonyl)amino group.[38,40] Therefore we turned our attention to the N,O-acylated 1-amino-4-oxy-substituted butadiene **15b** (Scheme VIII), which is readily obtained from pyridine via Zincke cleavage, pH-controlled aldehyde oxidation to δ-benzoyloxy pentadienoic acid and subsequent Curtius degradation of the carboxy group.[41] Again this compound was very useful in reactions with various CC-dienophiles (Scheme VIII) revealing an easy entry into the not yet developed cyclitol chemistry.[41] Compound **15b** turned out to be more reactive in hetero-Diels–Alder reactions with glyoxylates than any of the other two dienes (**11** and **15a**). This may be due to electron polarization because of different opposing 1,4-substituents.

As deducible from the acrylate addition product **17**, the wrong regioisomer was obtained with carbonyl

(35) Carlson, R. M.; Hill, R. K. *Org. Synth.* **1970**, *50*, 24.
(36) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1979**, *72*, 272; **1981**, *89*, 159.
(37) Schmidt, R. R.; Angerbauer, R. *Angew. Chem.* **1979**, *91*, 325; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 304.
(38) Schmidt, R. R.; Wagner, A. *Synthesis* **1981**, 273.
(39) Tanimoto, F.; Tanaka, T.; Kitano, H.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1922.
(40) Wagner, A. Dissertation, Universität Konstanz, 1983.
(41) Schmidt, R. R.; Wagner, A. *Synthesis* **1982**, 958.

Scheme VIII



dienophiles: the (ethoxycarbonyl)amino group was found in the 1-position and the benzoyloxy group in the 4-position of the pseudoglycals. Reasonable possibilities for reverting the regiochemistry of this reaction could be increasing the electron-withdrawing character of the amino substituent or increasing the electron donating character of the oxy substituent. We chose the second alternative and substituted the benzoyloxy group in compound **15b** by the *tert*-butyldimethylsilyl (TBDMS) group, affording the 1,3-diene **15c**.[42] This diene led to the desired pseudoglycal **18** when the more reactive *p*-nitrobenzyl glyoxylate was added as heterodienophile rather than the less reactive methyl glyoxylate (Scheme VIII). Transesterification with sodium methoxide/methanol and replacement of the TBDMS-group by the acetyl group provided compound **19**, which was ready for N-glycosidation with 2,4-bis((trimethylsilyl)oxy)-pyrimidine affording D,L-uracinine **20** (α:β ratio $\approx$ 1:2). The *p*-nitrobenzyl ester derivative of compound **19** gave exclusively the corresponding α-nucleosiduronate.[42]

1,4-Functionalization of 1,3-Dienes with Diheterodienophiles

To avoid CC-bond formation and concomitant functionalization via cycloaddition, an alternative approach to carbohydrates has been envisaged. An appropriately substituted diene having the required carbon skeleton may be transferred by epoxidation and nucleophilic ring opening or direct dihydroxylation or oxyamination into the desired target molecules. However, for pentose and hexose syntheses this approach has usually lacked high diastereoselectivity.[43] It was quite successfully applied by Achmatowicz to 2-alkyl furans, giving access to 4-functionalized hexoses,[44] and also in assisted stereoselective carbon–heteroatom bond formation, especially in Sharpless epoxidation.[45]

A hetero-Diels–Alder approach aimed at direct 1,4-functionalization of open-chain 1,3-dienes either in 1,4-, 2,5-, or 3,6-position is conceivable by reaction of singlet oxygen, nitroso compounds, and azodicarboxylates as dihetero-dienophiles with 1-oxy-1,3-dienes, 1-aldehydo-2,4-dienes, or 1-aldehydo-3,5-dienes, respectively (Scheme III, route D analyses the reaction of 1-oxy-1,3-dienes with singlet oxygen). For this purpose we first investigated azodicarboxylate addition to readily available 2,4-pentadienal acetal, which gave tetrahydropyridazine derivative **21** (Scheme IX).[46] Cis-dihydroxylation was diastereospecific and gave exclusively the ribo-configurated 3,4-dihydroxy hexahydropyridazine. As indicated in the box of Scheme IX exhibiting the preferred conformer of tetrahydropyridazine **21**, cis-dihydroxylation took place only from the less hindered site. Subsequent basic urethane hydrolysis, reductive NN-bond cleavage, and simple racemate resolution with tartrate liberated in very

(42) Schmidt, R. R.; Wagner, A. *Tetrahedron Lett.* **1983**, *24*, 4661.

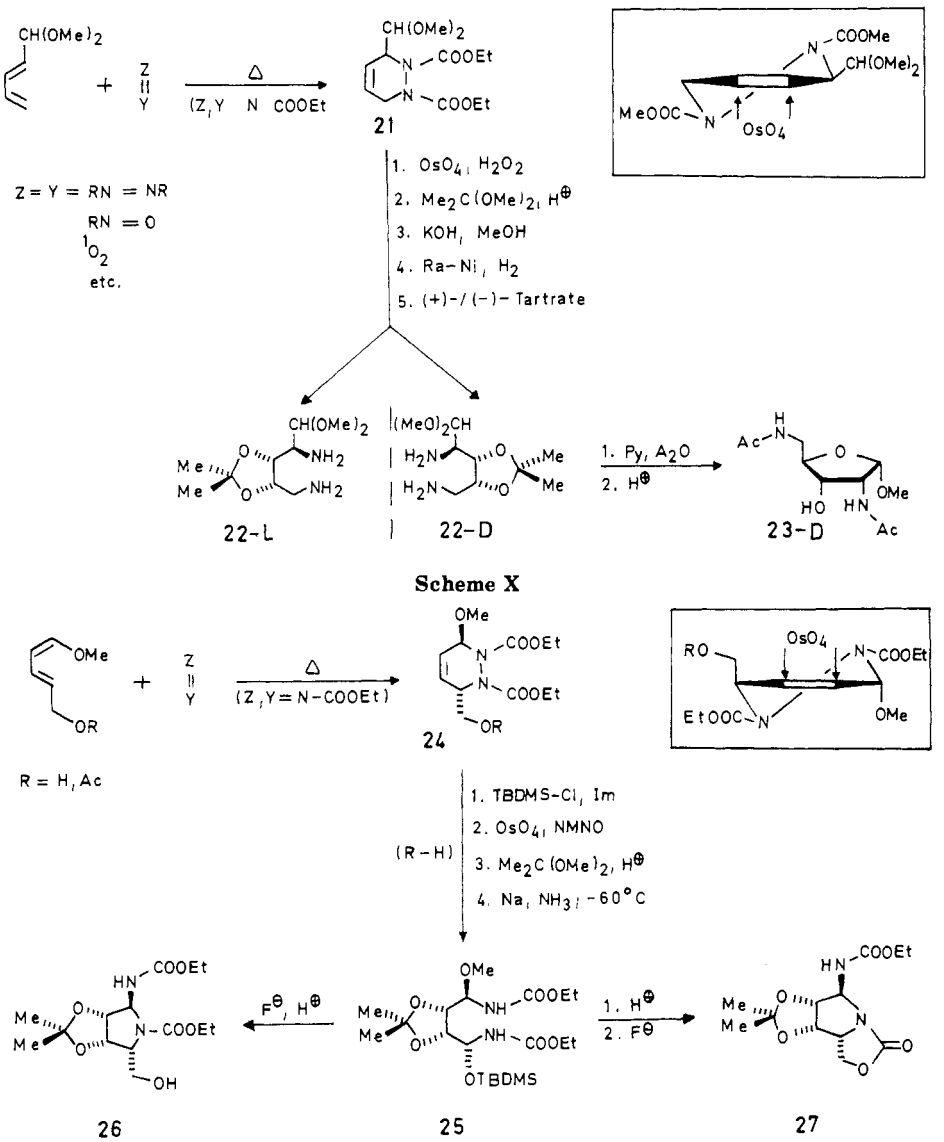
(43) (a) Reference 4, 3–30. (b) Reference 6, 152–170.

(44) Achmatowicz, O., Jr., Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. Achmatowicz, O., Jr.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.

(45) A breakthrough was Sharpless epoxidation of allylic alcohols: ref 5, 170–177.

(46) Schmidt, R. R.; Scheibe, R. *Liebigs Ann. Chem.* **1980**, 1307.

Scheme IX



Scheme X

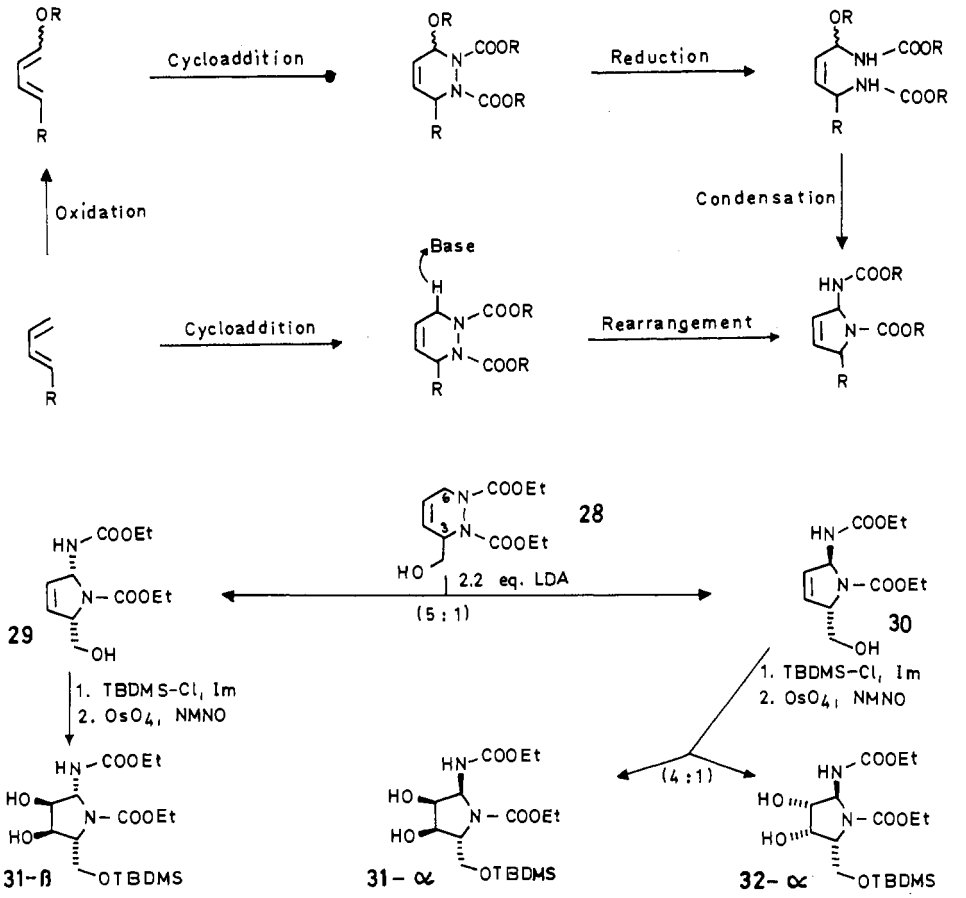
simple reactions with good yields the 2,5-diamino-2,5-dideoxy-D- and -L-ribose derivatives **22**-D/L, respectively. Furanoside **23**-D was obtained by acetylation and subsequent acid treatment.

Variation of the substitution pattern and of the relative stereochemistry is possible by starting from readily available 1-methoxy-1,3-pentadien-5-ols (Scheme X).[47] With azodicarboxylate the tetrahydropyridazines **24** were obtained. Protection of the 5-oxy substituent with the TBDMS group and cis-dihydroxylation of the C–C double bond with osmium tetraoxide *N*-methylmorpholine *N*-oxide (NMNO) afforded exclusively the *lyxo*-configurated 2,3-dihydroxy-hexahydropyridazine. As indicated in the box of Scheme X exhibiting the perferred conformer of compound **24** (R = TBDMS), the 1-methoxy substituent prevents α-site attack more than the 4-oxymethyl substituent β-site attack. This strong influence of 1-oxy substituents on site selectivity (and on reactivity, which is usually reduced) of pseudoglycals and corresponding compounds has already been observed for 1,4-dioxy substituted pseudoglycals (Scheme VII).[48] It is due to the operation of the anomeric and allylic effects. Protection of the 2,3-dihydroxyhexahydropyridazine intermediate and subsequent direct NN-bond cleavage with sodium in liquid ammonia afforded 4-amino-4-deoxy-D,L-lyxose **25**, which was easily converted into the corresponding pyrrolidine derivatives **26** and **27** upon exposure to fluoride in acidic solution or mild acid and subsequent fluoride treatment.

The introduction of a functional group at C-1 of butadiene and the reductive cleavage of the N–N bond in the approach exhibited in Scheme X would not be required if by cleaving the NN-bond the concomitant oxidation of this carbon atom to the aldehyde stage could be effected (Scheme XI).[17] In the Stevens rearrangement nitrogen ylids suffer a [1.2]-sigmatropic carbon shift from nitrogen to carbon. Therefore, carbanion formation α to a hydrazino or a hydroxylamino group could induce the required nitrogen shift from nitrogen to carbon, which has analogues in the Polonovski reaction and in the Wittig and Pummerer rearrangements. However, ease of deprotonation of the α-C–H bond, nucleophilicity of the generated carbanion, steric requirements for the rearrangement, and stabilization of the negative charge in the rearrangement product will be determining factors. In addition, elim-

(47) Forrest, A. K.; Schmidt, R. R.; Huttner, G.; Jibril, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1981.
(48) Angerbauer, R. Dissertation, Universität Konstanz, 1979.

Scheme XI



ination of functional groups at any stage has to be avoided, as it would annihilate the whole effort.[49]

The tetrahydropyridazine **28**, readily obtained from pentadienol and azodicarboxylate in high yield,[17] was an excellent substrate for this rearrangement (Scheme XI). Treatment with lithium diisopropylamide (LDA) gave the expected rearrangement products **29** and **30** as easily separable diastereoisomers (5:1 ratio). It was learned that the unprotected hydroxy group in tetrahydropyridazine **28**, which upon base addition forms the oxide prior to generating the carbanion at carbon-6, reduces the rate of 1,4-elimination to a 1-hydrazino-1,3-pentadiene derivative and this way favors the rearrangement reaction. However, preferred formation of compound **29** (β-derivative) cannot be deduced from the conformation of the starting material. This compound gave after O-protection upon cis-dihydroxylation diastereospecifically the expected D,L-*ribo*-pyrrolidine **31**-β having four adjacent chiral centers. The minor product (α-derivative) **30** reacted less selectively, giving the D,L-*ribo* isomer **31**-α and the D,L-*lyxo* isomer **32**-α. Surprisingly, the *lyxo* isomer did not predominate. Obviously many extensions of this reaction, including cycloadditions with singlet oxygen and nitroso compounds, are conceivable. The product would be of value for various highly functionalized natural product syntheses.

(49) For instance rearrangement of3,6-dihydro-1,2-oxazines and concomitant elimination leads to pyrroles: Firl, J.; Kresze, G. *Chem. Ber.* **1966**, *99*, 3695. Scheiner, P.; Chapman, O. L.; Lassila, J. D. *J. Org. Chem.* **1969**, *34*, 813.

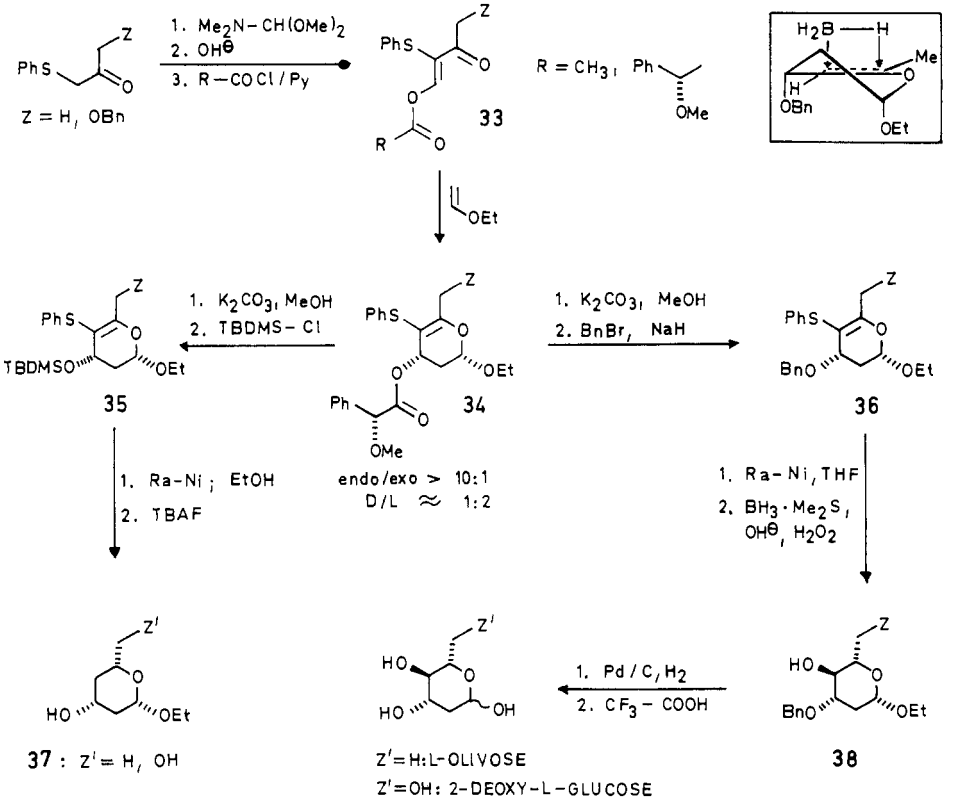
Inverse-Type Hetero-Diels-Alder Reactions with Functionally Substituted α,β-Unsaturated Carbonyl Compounds

Hetero-Diels–Alder reactions between 1,4-diheterosubstituted electron rich 1,3-dienes and reactive carbonyl compounds lead directly to pseudoglycals (5,6-dihydro-2*H*-pyrans), which are versatile intermediates for short carbohydrate syntheses (Scheme III, route B). Hetero-Diels–Alder reactions with inverse electron demand between α,β-unsaturated carbonyl compounds (1-oxa-1,3-dienes) and enol ethers as dienophiles are an attractive route for the synthesis of 3,4-dihydro-2*H*-pyrans.[13] However, this reaction is only of great potential for the preparation of carbohydrates and related highly functionalized natural products if further functional groups, especially electron donating hetero substituents, are compatible with this reaction (Scheme III, route E). In addition, not only enol ethers but also enediol ethers, ketene acetals, and alkyl-substituted derivatives must be substrates in these reactions which also require high diastereoselectivity. Most of these requirements will result in a strong decrease in reactivity.

Recent investigations have demonstrated that electron-withdrawing substituents at the α-position of α,β-unsaturated carbonyl compounds increase the rate of this reaction strongly.[50] Therefore, we first turned our

(50) Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023. Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 1133. Bitter, J.; Lettich, J.; Partale, H.; Polansky, O. E.; Reimer, W.; Ritter-Thomas, U.; Schlamann, B.; Stilkerieg, B. *Chem. Ber.* **1980**, *113*, 1020. Tietze, L.-F.; von Kiedrowski, G.; Harms, K.; Clegg, W.; Sheldrick, G. *Angew. Chem.* **1980**, *92*, 130; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 134.

Scheme XII



attention to α-methoxymethylene-substituted 1,3-dicarbonyl compounds as 1-oxa-1,3-dienes and, indeed, with enol ethers, enediol ethers, and ketene acetals, the expected 3,4-dihydro-2*H*-pyrans were obtained in high yield.[51-53] However, the endo/exo selectivity was very often low. In addition, removal of the CC-double bond and stereoselective functionalization at positions 5 and 6 (pyran numbering) caused difficulties.[52]

With the aim of using this method for the synthesis of carbohydrates and closely related compounds, a carbon substituent in the 4-position (5-position in pyran numbering) is redundant. Instead, a functional heterosubstituent is required as indicated already in the introductory section. However, β-alkoxy α,β-unsaturated carbonyl compounds having no electron-withdrawing substituent in the α-position are very unreactive towards enol ethers.[54] Therefore, we undertook investigations aimed at introducing a versatile functional substituent in the 4-position (5-position in pyran numbering), which (i) increases the rate and the diastereoselectivity of the cycloaddition reaction and (ii) enables a straightforward introduction of hydroxy, amino, methyl, hydrogen, and perhaps other subtituents in a diastereospecific manner. Results with β-acyloxy-α-phenylthio α,β-unsaturated carbonyl compounds **33** as heterodienes demonstrate that the phenylthio group fulfills these requirements (Scheme XII).[9,55] 4-Functionalization and derivatization in general is predisposed by the (phenylthio)enol ether structure.

The required 1-oxa-1,3-dienes **33** were obtained in a convenient efficient route from phenylthioacetone and derivatives (Scheme XII).[9,52,55] Reaction with enol ethers, enediol ethers, and especially ketene acetals went quite smoothly with high yields, and afforded exclusively or almost exclusively the *endo*-3,4-dihydropyran adduct. With the O-methyl mandeloyl group as chiral auxiliary, in addition, preferential formation of one enantiomer **34** (Z = H, OBn) could be achieved. As indicated in Scheme XII removal of the acyl group and protection of the 3-hydroxy group with either benzyl or *tert*-butyldimethylsilyl gave the corresponding 3,4-dihydropyran intermediates **35** and **36**, respectively, Z being a hydrogen atom or a benzyloxy group. Treatment of compounds **35** with Raney nickel in ethanol led to phenylthio group removal and immediate diastereospecific hydrogenation, providing after deprotection 2,4,6-trideoxy- and 2,4-dideoxy-L-*threo*-hexopyranosides **37** (Z' = H, OH). However, when compounds **36** (Z = H, OBn) were exposed to Raney nickel in tetrahydrofuran only the phenylthio group was replaced by hydrogen. The remaining C–C double bond was available for cis-specific borane addition and subsequent stereocontrolled hydroxy group introduction with hydrogen peroxide, providing diastereospecifically the 2,6-dideoxy- and the 2-deoxy-L-*arabino*-hexopyranosides **38** (Z = H, OBn). As indicated in the box of Scheme XII, due to the anomeric and allylic effect one conformer is preferred in compounds **36** and **35** which is diastereospecifically attacked by the borane reagent (or by Raney nickel) from the less hindered site. Compound **38** with Z being hydrogen was easily con-

(51) Schmidt, R. R.; Maier, M. *Tetrahedron Lett.* **1982**, *23*, 1789.

(52) Maier, M.; Schmidt, R. R. *Chem. Ber.* **1985**, *118*, 2261.

(53) Similar reactions with enol ethers were carried out independently: Tietze, L. F.; Glüsenkamp, K. H.; Hanus, K.; Remberg, G. *Tetrahedron Lett.* **1982**, *23*, 1147. Tietze, L. F.; Glüsenkamp, K. H. *Angew. Chem.* **1983**, *95*, 901; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 887.

(54) Berti, G.; Catelani, G.; Colonna, F.; Monti, L. *Tetrahedron* **1982**, *38*, 3067.

(55) Maier, M. Dissertation, Universität Konstanz, 1985.

verted into known L-olivose,[9] and compound **38** with Z being benzyloxy gave via the same route 2-deoxy-L-glucose.[55,56]

Thus the inverse-type hetero-Diels–Alder reaction based hexopyranoside and hexopyranose synthesis is high yielding, and it allows the diastereospecific generation of up to four chiral centers. Concomitant stereocontrolled generation of a fifth chiral center in the 2-position (3-position in pyran numbering) is under investigation. The direct access to partially O-protected derivatives with different O-protecting groups is an additional advantage of this method because carbohydrates are usually required for regioselective glycoside bond formation.

Concluding Remarks

Attempts to synthesize 1,4-functional pentoses and hexoses via a Diels–Alder approach with furans as the precursor are most preferable over 7-oxanorbornene intermediates. Application of the meso trick and selective C–C bond cleavage are further elements constituting a convenient entry to different carbohydrate systems. 1,3-Butadienes having electron donating 1,4-dihetero substituents are not only valuable intermediates for CC-dienophiles and subsequent cyclitol syntheses, they are also reactive in hetero-Diels–Alder reactions with glyoxylates, affording interesting pseudoglycal uronates useful in various further modifications. Direct stereocontrolled 1,4-functionalization of 1,3-dienes having a C-1 or C-4 carbon substituent is accomplished efficiently by hetero-Diels–Alder reaction with diheterodienophiles and subsequent tandem hetero–hetero atom bond cleavage and oxido reduction. This reaction should have a wide range of further applications.

Especially rewarding is inverse-type hetero-Diels–Alder reaction with highly functionalized 1-oxa-1,3-dienes, which are readily available by simple synthetic procedures. Cycloaddition with electron rich dienophiles and functionalization of the dihydro-pyran double bond is highly diastereoselective, giving convenient entries to 2-deoxy, 2,4- and 2,6-dideoxy, and 2,4,6-trideoxy hexoses having in addition selective oxygen protection. This synthetic design envisages efficient extensions to other natural product types having dihydro- and tetrahydropyran precursors.

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(56) Schmidt, R. R.; Haag, B., unpublished.