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Synthesis of Fused Cyclic Systems Containing Medium-Sized Rings through Tandem ROM-RCM of Norbornene Derivatives Embedded in a Carbohydrate Template

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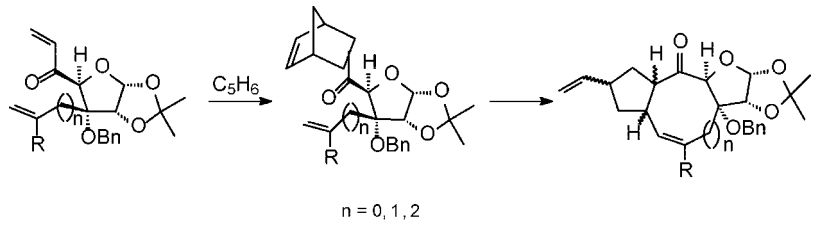

A general approach for the synthesis of fused cyclic systems containing medium-sized rings (7−9) has been developed. The key steps involve a diastereoface-selective Diels−Alder reaction of the dienophiles **4a**−**d** attached to a furanosugar with cyclopentadiene and ring opening (ROM)-ring closing metathesis (RCM) of the resulting norbornene derivatives **10a**−**d** and **11a**−**d**. Diels−Alder reaction of the dienophiles **4a**−**d** with cyclopentadiene in the absence of a catalyst produced **10a**−**d** as the major product arising through addition of the diene to the unhindered *Si*-face. The most interesting and new aspect of the Diels−Alder reaction of these dienophiles is the accessibility of the *Re*-face that was blocked by the alkenyl chains under Lewis acid catalysis producing the diastereoisomers **11a**−**d** exclusively. The reversal of facial selectivity from an uncatalyzed reaction to a catalyzed one is unprecedented. The observed stereochemical dichotomy is attributed to rotation of the enone moiety along the σ bond linking the sugar moiety during formation of the chelate **13**. This makes the *Re*-face of the enone moiety in **4a**−**d** unhindered. Diels−Alder reaction of the carbocyclic analogue **15** under Lewis acid catalysis produced a 1:1 mixture of the adducts **16** and **17** confirming the participation of sugar ring oxygen in chelate formation. Finally ROM-RCM of **10a**−**d** and **11a**−**d** with Grubbs' catalyst afforded the *cis-syn-cis* and *cis-anti-cis* bicyclo-annulated sugars **21a**−**d** and **23a**−**d**, respectively, containing 7−9 membered rings.

Introduction

Fused bi- and tricyclic systems containing medium sized rings (7−9) are frequently encountered in biologically active natural products. Development of new synthetic approaches to these ring systems thus continues to be an important goal in organic synthesis. Toward this endeavor a number of elegant strategies have been developed.[1] Annulation of medium rings onto a pre-existing ring is generally employed for this purpose. However, a single-step method for the direct construction of these systems is especially attractive due to its brevity and diastereoselectivity. A number of strategies involving intramolecular [4+2],[2] [4+3],[3] and [4+4][4] cycloaddition reactions have been reported for direct

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construction of fused cyclic systems with either seven- or eight-membered rings only.

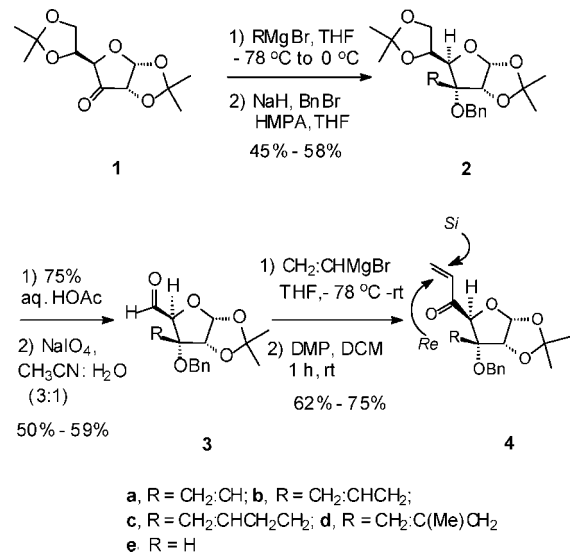
Since the pioneering work from the groups of Grubbs and Schrock, RCM[5]reaction of dienes and enynes has emerged as a powerful tool for the synthesis of rings of different sizes, especially medium-sized rings which are difficult to make by other methods. For example, a tandem RCM of dienynes has been employed for the synthesis of fused bicycles containing seven-membered[6] as well as eight-membered[7] rings. Another metathesis-based strategy developed by Grubbs and co-workers[8] to construct fused bicycles involves a tandem ROM-RCM of appropriately constructed bicyclo[2.2.1]heptenes. Subsequent to this observation, there are reports of the synthesis of fused bicycles with common rings using tandem ROM-RCM of norbornene derivatives along with its application in natural products synthesis.[9] However, ROM-RCM of norbornene derivatives to construct fused bicycles with medium-sized rings is relatively less explored and restricted to the synthesis of structurally simple systems with seven- and eight-membered rings only.[10] Synthesis of nine-membered carbocyclic rings through RCM is difficult to achieve and to date there is only one successful attempt.[11]

In connection to our interest[12] in the synthesis of chiral target molecules from carbohydrates, we initiated an investigation on ROM-RCM of norbornene derivatives embedded in a furano-sugar with the following objectives: to determine the influence of an intervening sugar unit on the efficiency of ROM-RCM and to develop a strategy for the synthesis of chirally pure fused cyclic systems with seven-, eight-, and nine-membered rings. The results of this investigation are presented here.

Results and Discussion

To incorporate a sugar unit with an alkene chain into norbornene derivatives required for investigating ROM-RCM, Diels−Alder reaction of dienophiles **4** with cyclopentadiene was invoked. The required dienophiles were prepared from D-glucofuranose derivative **1** as illustrated by the synthesis of **4a** (Scheme 1).

SCHEME 1. Synthesis of Dienophiles 4a−e



Addition of vinyl magnesium bromide to the ketone **1**[13] followed by protection of the resulting carbinol gave the benzyl ether **2a**. The 5,6-isopropylidine unit in **2a** was selectively removed by treatment with aqueous acetic acid at room temperature. Periodate cleavage of the resulting diol gave the aldehyde **3a**. Addition of vinyl magnesium bromide to the aldehyde **3a** followed by Dess−Martin periodinane (DMP) oxidation afforded the enone **4a** in excellent yield. In a similar fashion the dienophiles **4b−d** were prepared by addition of appropriate alkenyl magnesium halides to the ketone **1**. The same protocol was used to prepare the dienophile **4e** from the compound **2e**.

Reaction of dienophiles **4** with cyclopentadiene is expected to give rise to four diastereoisomers arising through the endo and exo mode of addition from *Re* and *Si* faces. In connection to asymmetric Diels−Alder reaction, it was demonstrated[14] that face discrimination could be achieved by blocking one face of the enone by a bulky substituent. In the dienophiles **4** the front face (*Re*-face) is blocked by a *syn* alkyl substituent (R) on the center next to the side chain bearing the enone unit. Thus, it is expected that dienes will add to the dienophiles **4** preferentially from the unhindered *Si*-face. Except for a few reports[15] on Diels−Alder reaction of acrylates derived from carbohydrates as removable chiral auxiliaries, there is hardly any investigation[16] on Diels−Alder reaction of dienophiles related to **4**.

To determine the facial selectivity, the dienophiles **4** were initially subjected to Diels−Alder reaction with 2,3-dimethylbutadiene (DMB) (Scheme 2). This eliminates the possibility of formation of regio- and endo/exo isomers. Cycloaddition was carried out by heating a solution of the enones in toluene with

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SCHEME 2. Diels−Alder Reaction of 4 with DMB

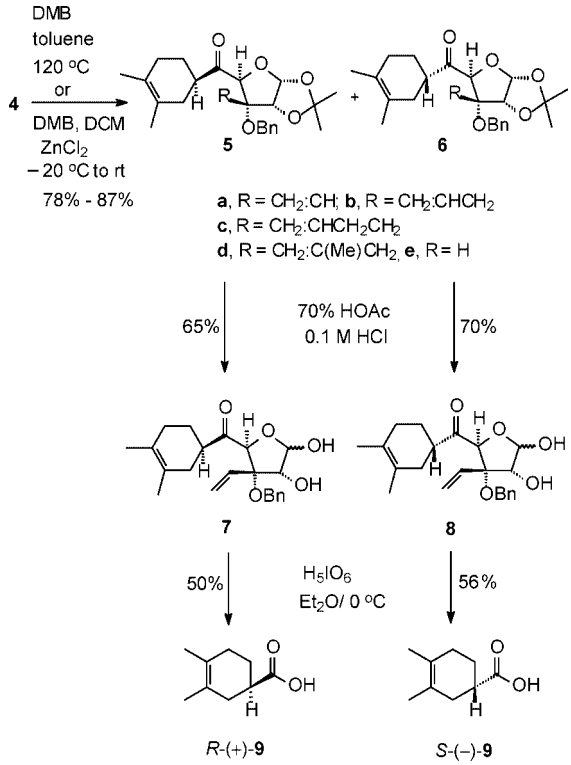

TABLE 1. Diels−Alder Reaction of Enones 4 with DMB

entry	dienophile	products	yeild (diastereomeric ratio)
1	**4a**	**5a** + **6a**	83% (2:1)[a] 81% (1:100)[b]
2	**4b**	**5b** + **6b**	85% (2:1)[a] 80% (1:100)[b]
3	**4c**	**5c** + **6c**	88% (2:1)[a] 78% (1:100)[b]
4	**4d**	**5d** + **6d**	86% (6:1)[a] 82% (1:100)[b]
5	**4e**	**5e** + **6e**	80% (1:1)[a] 87% (1:1)[b]

[a] Toluene, 120 °C. [b] $ZnCl_2$, DCM, −20 °C to rt.

DMB in a sealed tube at 120 °C. The results are summarized in Table 1. The enone **4a** afforded a mixture of adducts **5a** and **6a** in 83% yield in a ratio of 2:1 (entry 1).

Increasing the chain length of the substituent "R" from vinyl to allyl or homoallyl did not have any effect on the stereochemical outcome. The enones **4b** and **4c** gave the diastereoisomeric pairs **5b**, **6b** and **5c**, **6c**, respectively, in almost similar ratios (2:1) (entries 2 and 3). However, a significant increase in the ratio (6:1) of the diastereoisomers **5d** and **6d** (entry 4) was observed on replacing vinyl or allyl in the dienophile **4** by a branched alkene such as methallyl demonstrating that increasing bulk of the substituent has a significant effect in diastereoface selection. Structural assignment to these adducts followed from the following transformations. The adduct **6a**, obtained exclusively from the $ZnCl_2$ catalyzed reaction of the dienophile **4a** with DMB (vide infra), was treated with acetic acid containing a catalytic amount of HCl to provide an anomeric mixture of the diols **8** in 70% yield. Treatment of the mixture of these diols with periodic acid afforded in 56% yield the known[17] carboxylic acid *S*-(−)-**9**, $[\alpha]^{25}_D$ − 81.4 (*c* 0.0153, EtOH) [lit.[17] $[\alpha]^{25}_D$ −85 (*c* 1.8, EtOH) (ee 99%)]. Thus the adduct from which the carboxylic acid *S*-(−)-**9** was derived possesses the structure **6a**. In a similar fashion the inseparable mixture (ca. 2:1) of adducts **5a** and **6a** obtained under noncatalyzed condition was degraded through the mixture of diols **7** and **8** to provide the *R*-(+)-carboxylic acid **9**, $[\alpha]^{26}_D$ + 30 (*c* 0.0158, EtOH). The sign of the specific rotation of the carboxylic acid establishes the structure of the major adduct in the mixture as **5a**. The magnitude of the specific rotation observed for *R*-(+)-**9** when compared with that reported for *S*-(−)-**9** is in conformity with about a 2:1 ratio of the adducts **5a** and **6a** obtained in the noncatalyzed reaction. Structures of adducts **5b−e** and **6b−e** were based on analogy to the formation of compounds **5a** and **6a** from Diels−Alder reaction of the dienophile **4a** with DMB.

SCHEME 3. Diels−Alder Reaction of 4 with C_5H_6

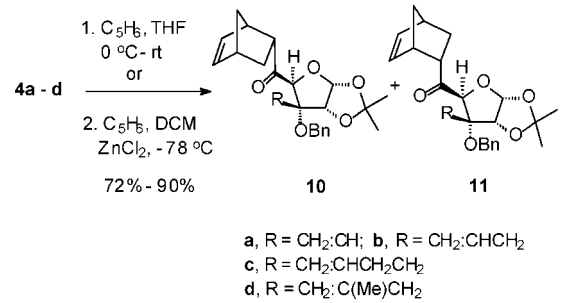

TABLE 2. Diels−Alder Reaction of Enones 4 with Cyclopentadiene

entry	dienophile	products	yeild (diastereomeric ratio)
1	**4a**	**10a** + **11a**	88% (3:1)[a] 84% (1:100)[b]
2	**4b**	**10b** + **11b**	89% (4:1)[a] 86% (1:100)[b]
3	**4c**	**10c** + **11c**	89% (4:1)[a] 87% (1:100)[b]
4	**4d**	**10d** + **11d**	90% (16:1)[a] 88% (1:100)[b]

[a] THF, 0 °C. [b] $ZnCl_2$, DCM, −78 °C.

Diels−Alder reaction of the dienophiles **4a−d** with cyclopentadiene was then investigated (Scheme 3). The results are summarized in Table 2. Unlike the reaction with DMB, with cyclopentadiene an improved diastereoface selectivity was observed in all cases. No exoadduct was formed. The dienophile **4a** on reaction with cyclopentadiene in THF at 0 °C afforded a mixture of the endoadducts **10a** and **11a** in 3:1 ratio (entry 1, condition "a"). With a longer alkenyl chain such as allyl and homoallyl (entries 2 and 3), the ratio of the diastereoisomeric products increased to 4:1. However, a Me substituent on the alkene unit dramatically increased the ratio of products **10d** and **11d** to 16:1 (entry 4). The structure of the major adduct **10d** was determined through single crystal X-ray.[18]

Thus the minor adduct obtained in the reaction of **4d** was assigned structure **11d**. The major and minor adducts from Diels−Alder reaction of **4a−c** were assigned structures **10a−c** and **11a−c**, respectively, in analogy to the formation of **10d** and **11d** from **4d**. The X-ray structure of adduct **10d** revealed

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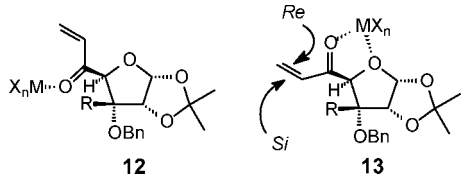
(18) Crystallographic data for compound **10d** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 680372. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223-336033. E-mail: deposit@ccdc.cam.ac.uk.

that cyclopentadiene added to the unhindered *Si*-face of dienophile **4d** through *s-cis* conformation of the enone as depicted in structure **4**.

Lewis acid catalysts have profound influence on diastereoface discrimination in the Diels−Alder reaction through formation of a chelate that rigidly holds the enone moiety with one face shielded by a neighboring substituent.[14] Improved diastereoselectivities were observed in such cases compared to the noncatalyzed reactions resulting in the formation of one diastereoisomer predominantly. However, this approach fails to provide the diastereoisomer arising by addition of the diene to the face blocked by the substituent. Helmchen and co-workers[19] and later on Waldmann[20] demonstrated that both diastereomeric adducts could be obtained depending on the nature of the Lewis acid employed in the Diels−Alder reaction of acrylates/acrylamides with appropriately designed chiral auxiliaries. A Lewis acid capable of undergoing chelation with a neighboring heteroatom in the auxiliary forms a rigidly held complex. This complex shields one face of the enone and produces one diasteroisomer predominantly. On the other hand, a Lewis acid incapable of chelation produces the other diastereoisomer. In these examples the coordinated Lewis acid itself blocks one face and the substituent at the chiral center in the auxiliary makes no significant contribution to the diastereoface differentiation.[19]

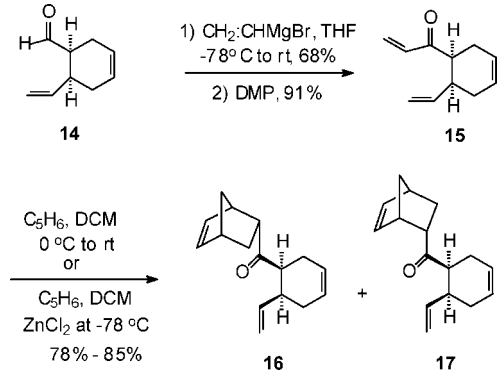
In light of the above observations, we became interested in investigating the Lewis acid catalyzed Diels−Alder reaction of the dienophiles **4** in order to explore the influence of Lewis acid on the stereochemical outcome. We visualized that the σ bond linking the enone moiety in the Lewis acid (MX_n)-complexed dienophile **12** would rotate due to increased eclipsing interaction with the substituent R and undergo chelation with the sugar ring oxygen to form a rigid bidentate chelate complex **13**. In this complex the *Si*-face is blocked by the substituent "R". Addition is then expected to take place on the *Re*-face eventually resulting in reversal of facial selectivity. Gratifyingly, the facial selectivity in the Diels−Alder reaction of the dienophiles **4a**−**d** could be reversed with Lewis acid. After considerable experimentation with a number of Lewis acids, $ZnCl_2$ turned out to be the best catalyst in reversing the facial selectivity. Thus reaction of enones **4a**−**d** with DMB in toluene at 0 °C in the presence of $ZnCl_2$ afforded almost exclusively adducts **6a**−**d** (Table 1). Similarly reaction of **4a**−**d** with cyclopentadiene in the presence of $ZnCl_2$ gave exclusively adducts **11a**−**d** (Table 2, condition "b"), respectively. Thus under noncatalyzed condition dienes added preferentially to the *Si*-face as the *Re*-face was blocked by the substituent "R" while with the $ZnCl_2$, reaction presumably proceeded through the chelated complex **13** (M = Zn) in which the *Si*-face was blocked by "R". The Lewis acid in these examples is simply changing the orientation of the *Re*-face of the enone from hindered to unhindered through rotation during formation of the chelate.



12 **13**

That the substituent "R" is responsible for face discrimination under both catalyzed and noncatalyzed reactions is demonstrated by reaction of the enone **4e** with DMB to produce a 1:1 mixture of the adducts **5e** and **6e** under both conditions. Involvement of sugar ring oxygen in metal chelate formation in the Diels−Alder reaction of dienophiles attached to the sugar unit resulting in reversal of facial selectivity is unprecedented.

SCHEME 4. Synthesis and Diels−Alder Reaction of 15



14 **15** **16** **17**

To understand the role of sugar ring oxygen in reversing the face selectivity, the Diels−Alder reaction of the carbocyclic analogue **15** was investigated. The dienophile **15** was prepared from the aldehyde **14**[21] by addition of vinyl magnesium bromide followed by oxidation of the resulting carbinol (Scheme 4).

As expected, reaction with cyclopentadiene without catalyst gave an inseparable mixture of adducts **16** and **17** in 2.8:1 ratio. With $AlCl_3$ or $ZnCl_2$ the same products were formed in ca. 1:1 ratio. This investigation clearly demonstrates that the ring oxygen in the carbohydrate unit in dienophiles **4** was involved in reversing the selectivity in the $ZnCl_2$ catalyzed Diels−Alder reaction. Thus the sugar moiety in dienophiles **4**, under noncatalyzed and catalyzed conditions, led the enone unit to adopt two different orientations so as to expose either the *Si*-face or the *Re*-face selectively for Diels−Alder addition.

ROM-RCM of the bicyclo[2.2.1]heptene derivatives was next investigated (Scheme 5). Treatment of compound **10a** in dichloromethane in the presence of catalyst **18** under ethylene atmosphere led to complete disappearance of the starting material within 1 h. The product obtained in 92% yield was characterized as ring-opened product **20a**. Attempted ROM-RCM of **10a** under identical conditions with the more reactive catalyst **19** caused extensive polymerization of the norbornene derivatives.

However, when ring-opened product **20a** was treated with catalyst **19**, smooth ring closure took place in 6 h to produce oxa-tricycle **21a** in 86% yield. On the basis of the above observation, the following protocol was used to accomplish ROM-RCM. The norbornene derivatives were first treated with catalyst **18** until the disappearance of the starting materials (1−1.5 h) (TLC). At this stage, in each case except **10c** and **11b**, analysis of an aliquot of the reaction mixture showed the presence of the ROM products **20a**,**b**,**d** and **22a**,**c**,**d** only. To this reaction mixture catalyst **19** was then added and the reaction was continued until the ROM product disappeared. In this way the norbornene derivatives **10a**,**b**,**d** and **11a**,**c**,**d** afforded respectively the bicyclo-annulated products **21a**,**b**,**d** and **23a**,**c**,**d** in very good yields. Compounds **10c** and **11b** gave directly the

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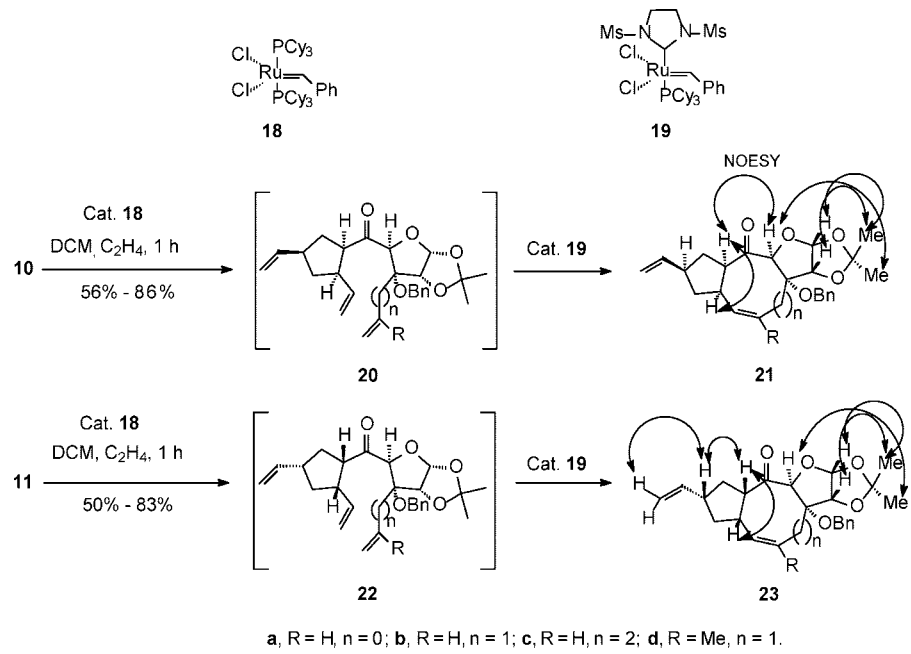
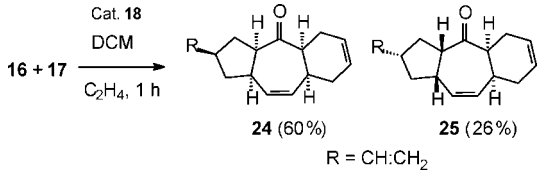
SCHEME 5. ROM-RCM of Norbornene Derivatives 10 and 11



a, R = H, n = 0; **b**, R = H, n = 1; **c**, R = H, n = 2; **d**, R = Me, n = 1.

SCHEME 6. ROM-RCM of 16 and 17



nine-membered and eight-membered carbocyclic derivatives **21c** and **23b**, respectively, in 1 h with catalyst **18**. The structures of products **21a** and **23a** were ascertained through analysis of their NMR (^{1}H, ^{13}C, and NOESY) spectra.

After successfully accomplishing ROM-RCM of the norbornene derivatives to construct fused oxa-tricycles, we became interested in exploring the reactivity of **16** and **17** which do not have an oxygen atom in the neighboring ring. Under the above reaction condition, the inseparable mixture of adducts **16** and **17** afforded the *cis-syn-cis* and *cis-anti-cis* 5−7−6 tricycles **24** and **25** in 60% and 26% isolated yields, respectively (Scheme 6). Direct synthesis of 5−7−6 tricyclic systems is of great significance as this unit represents the core structure of a number of highly biologically active natural products.[22]

In conclusion, we have demonstrated that the carbohydrate ring when attached to an acyclic dienophile, under appropriate reaction condition, can direct addition of dienes either to the *Si*-face or to the *Re*-face enabling synthesis of both diastereoisomeric adducts. This face-selective Diels−Alder reaction of the dienophiles with cyclopentadiene in combination with ROM-RCM of the resulting norbornene derivatives offers a general expedient approach for the synthesis of densely functionalized bicyclo-annulated sugars with seven-, eight-, and nine-membered[23] rings. The most notable feature of the present protocol is the construction of both *cis-syn-cis* and *cis-anti-cis* bicyclo-annulated sugars. The bicyclo-annulated sugars thus obtained will be of considerable synthetic potential as the carbohydrate ring can either be converted to a carbocycle[16] to produce linearly fused tricyclic systems or cleaved[24] to afford fused bicyclic systems.

Experimental Section

Diels−Ader Reactions of Dienophile 4a with DMB. ((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)tetrahydro-2,2-dimethyl-6-vinylfuro[2,3-*d*][1,3]dioxol-5-yl)((*S*)-3,4-dimethylcyclohex-3-enyl)methanone (5a). A mixture of the dienophile **4a** (70 mg, 0.21 mmol), DMB (0.1 mL, 0.89 mmol), and a catalytic amount of hydroquinone in toluene (2 mL) was heated at 120 °C for 3 h in a sealed tube. The solvent was evaporated under reduced pressure to afford an inseparable mixture of cycloadducts **5a** and **6a** (72 mg, 83%) in 2:1 ratio (by NMR), $[\alpha]^{25}_{D}$ + 61.3 (*c* 7.8, $CHCl_3$); IR ν_{max} 1718 cm^{-1}; ^{1}H NMR (of the mixture) δ 1.40 (3H, s), 1.45−1.54 (1H, m), 1.59 (6H, s), 1.62 (3H, s), 1.81−2.09 (4H, m), 2.18−2.27 (1H, m), 2.95−3.05 (1H, m), 4.62−4.68 (2H, m), 4.74−4.77 (1H, m), 4.92−4.99 (1H, m), 5.31 (1H, d, J = 17.7 Hz), 5.42 (1H, d, J = 11.2 Hz), 5.63−5.74 (1H, m), 5.97 (1H, d, J = 3.3 Hz), 7.27−7.39 (5H, m); ^{13}C NMR (for the major isomer **5a** from the mixture) δ 18.9 (CH_3), 19.1 (CH_3), 26.5 (CH_2), 26.7 (CH_3), 27.1 (CH_3), 31.5 (CH_2), 32.2 (CH_2), 44.8 (CH), 67.3 (CH_2), 81.4 (CH), 84.9 (CH), 86.1 (C), 104.4 (CH), 113.4 (C), 119.3 (CH_2), 124.2 (C), 124.9 (C), 127.01 (CH), 127.5 (CH), 128.3 (CH), 133.7 (CH), 138.3 (C), 208.7 (CO); HRMS (ESI) *m*/*z* (M + Na)$^+$ calcd for $C_{25}H_{32}O_5Na$ 435.2148, found 435.2140.

Diels−Alder Reaction of Dienophile 4a with Cyclopentadiene. ((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)dihydro-2,2-dimethyl-6-vinyl-5*H*-furo[3,2-ol][1,3]dioxol-5-yl)(bicyclo[2.2.1]hept-5-en-2yl)methanone (10a) and ((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)dihydro-2,2-dimethyl-6-vinyl-5*H*-furo[3,2-*d*][1,3]dioxol-5yl)(bicyclo[2.2.1]hept-5-en-2yl)methanone (11a). To a stirred solution of dienophile **4a**

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(24) Cf.: Haque, A.; Panda, J.; Ghosh, S. *Indian J. Chem.* **1999**, *38B*, 8.

(100 mg, 0.30 mmol) in dry THF (3 mL) at 0 °C was added freshly distilled cyclopentadiene (140 mg, 3.03 mmol) dropwise. Stirring was continued for 1 h at 0 °C and 5 h at rt. Solvent was removed in vacuo and the residue was purified by column chromatography to afford the cycloadduct **10a** (75 mg, 62%) and **11a** (30 mg, 26%). **10a**: colorless liquid, $[\alpha]^{26}_D$ +74.0 (*c* 1.75, $CHCl_3$); IR ν_{max} 1720 cm^{-1}; ^1H NMR δ 1.25 (1H, d, J = 7.8 Hz), 1.32−1.36 (2H, m), 1.39 (3H, s), 1.61 (3H, s), 1.74−1.82 (1H, m), 2.86 (1H, br s), 3.67 (1H, br s), 3.29−3.32 (1H, m), 4.60−4.73 (4H, m), 5.30 (1H, d, J = 17.8 Hz), 5.42 (1H, d, J = 11.3 Hz), 5.73 (1H, dd, J = 11.4, 17.7 Hz), 5.87 (1H, dd, J = 2.9, 5.3 Hz), 5.96 (1H, d, J = 3.4 Hz), 6.11 (1H, dd, J = 2.9, 5.4 Hz), 7.28−7.41 (5H, m); ^{13}C NMR δ 26.8 (CH_3), 27.1 (CH_3), 29.1 (CH_2), 42.8 (CH), 45.7 (CH), 49.2 (CH), 49.9 (CH_2), 67.3 (CH_2), 81.5 (CH), 85.7 (CH), 86.0 (C), 104.5 (CH), 113.4 (C), 119.3 (CH_2), 127.1 (CH), 127.5 (CH), 128.4 (CH), 132.5 (CH), 134.2 (CH), 137.1 (CH), 138.5 (C), 207.2 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{24}H_{28}O_5Na$ 419.1834, found 419.1838. **11a**: $[\alpha]^{26}_D$ +22.0 (*c* 1.8, $CHCl_3$); IR ν_{max} 1710 cm^{-1}; ^1H NMR δ 1.27 (1H, d, J = 7.7 Hz), 1.41 (4H, s), 1.50−1.56 (1H, m), 1.64 (3H, s), 1.67−1.69 (1H, m), 2.88 (1H, br s), 3.31 (1H, br s), 3.34−3.37 (1H. m), 4.67 (2H, d, J = 11.5 Hz), 4.79 (1H, d, J = 11.3 Hz), 4.96 (1H, s), 5.31 (1H, d, J = 17.7 Hz), 5.40 (1H, d, J = 11.2 Hz), 5.66 (1H, dd, J = 11.2, 17.6 Hz), 5.80 (1H, dd, J = 2.4, 5.4 Hz), 5.95 (1H, d, J = 3.3 Hz), 6.17 (1H, dd, J = 3, 5.4 Hz), 7.29−7.42 (5H, m); ^{13}C NMR δ 26.8 (CH_3), 27.2 (CH_3), 27.6 (CH_2), 42.9 (CH), 47.2 (CH), 48.9 (CH), 50.3 (CH_2), 67.3 (CH_2), 81.4 (CH), 85.4 (CH), 86.1 (C), 104.3 (CH), 113.3 (C), 119.2 (CH_2), 126.9 (CH), 127.6 (CH), 128.4 (CH), 130.9 (CH), 133.6 (CH), 138.1 (CH), 138.4 (C), 204.9 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{24}H_{28}O_5Na$ 419.1834, found 419.1837.

Lewis Acid Catalyzed Diels−Alder Reactions of Dienophile 4a with DMB. ((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)tetrahydro-2,2-dimethyl-6-vinylfuro[2,3-*d*][1,3]dioxol-5-yl)((*R*)-3,4-dimethylcyclohex-3-enyl)methanone (6a). To a magnetically stirred solution of the dienophile **4a** (60 mg, 0.18 mmol) in DCM (4 mL) at −20 °C was added $ZnCl_2$ (47 mg, 0.34 mmol) then the mixture was stirred for 15 min followed by addition of DMB (0.05 mL, 0.44 mmol). After being stirred for an additional 1 h, the reaction mixture was allowed to attain rt and quenched with brine (0.5 mL) then worked up in the usual way to afford after column chromatography the adduct **6a** (62 mg, 83%): $[\alpha]^{25}_D$ +34.3 (*c* 6.2, $CHCl_3$); IR ν_{max} 1717 cm^{-1}; ^1H NMR δ 1.40 (3H, s), 1.46 (1H, m), 1.59 (6H, s), 1.62 (3H, s), 1.75−1.86 (1H, m), 1.96−2.09 (4H, m), 2.97−3.03 (1H, m), 4.67 (2H, s), 4.75 (1H, d, J = 11.3 Hz), 4.91 (1H, s), 5.31 (1H, d, J = 17.7 Hz), 5.41 (1H, d, J = 11.2 Hz), 5.64−5.73 (1H, m), 5.96 (1H, d, J = 3.4 Hz), 7.27−7.38 (5H, m); ^{13}C NMR δ 18.9 (CH_3), 19.1 (CH_3), 24.5 (CH_2), 26.7 (CH_3), 27.1 (CH_3), 31.2 (CH_2), 34.1 (CH_2), 44.8 (CH), 67.2 (CH_2), 81.4 (CH), 85.2 (CH), 86.2 (C), 104.4 (CH), 113.4 (C), 119.3 (CH_2), 124.1 (C), 125.5 (C), 126.9 (CH), 127.5 (CH), 128.4 (CH), 133.8 (CH), 138.3 (C), 209.1 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{25}H_{32}O_5Na$ 435.2148, found 435.2148.

Lewis Acid Catalyzed Diels−Alder Reaction of Dienophile 4a with Cyclopentadiene. ((3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)dihydro-2,2-dimethyl-6-vinyl-5*H*-furo[3,2-*d*][1,3]dioxol-5yl)(bicyclo[2.2.1]hept-5-en-2yl)methanone (11a). To a magnetically stirred solution of dienophile **4a** (85 mg, 0.26 mmol) in DCM (5 mL) at − 78 °C was added $ZnCl_2$ (140 mg, 1.06 mmol) then the mixture was stirred for 15 min followed by addition of freshly distilled cyclopentadiene (103 mg, 1.56 mmol). After being stirred for 3 h, the reaction mixture was quenched with brine (0.5 mL) and worked up in the usual way to afford after column chromatography the adduct **11a** (85 mg, 84%). The spectral data of this compound are identical with those of the compound obtained above in the noncatalyzed reaction.

General Procedure for Metathesis. The general procedure for metathesis is illustrated by the synthesis of bicyclo-annulated sugar **21a**. A magnetically stirred solution of the compound **10a** (100 mg, 0.25 mmol) in DCM (50 mL) at −78 °C was saturated by purging ethylene through it. After 30 min the catalyst **18** (15 mg, 0.018 mmol, 7 mol%) was added and stirring was continued. After 1 h TLC of the reaction mixture indicated complete disappearance of the starting material. Removal of solvent from an aliquot of the reaction mixture revealed it to be the ring opened product **20a** only (6 mg): $[\alpha]^{24}_D$ +28.4 (*c* 1.8, $CHCl_3$); IR ν_{max} 1710 cm^{-1}; ^1H NMR δ 1.44−1.47 (1H, m), 1.36 (3H, s), 1.57 (3H, s), 1.76−1.83 (2H, m), 1.91−2.02 (1H, m), 2.43−2.57 (1H, m), 2.93−3.05 (1H, m), 3.48−3.57 (1H, m), 4.52 (1H, s), 4.58−4.69 (3H, m), 4.87−4.93 (2H, m), 5.01 (2H, d, J = 17.0 Hz), 5.32 (1H, d, J = 17.8 Hz), 5.38 (1H, d, J = 11.3 Hz), 5.67 (3H, m), 5.93 (1H, d, J = 3.3 Hz), 7.25−7.42 (5H, m); ^{13}C NMR δ 26.9 (CH_3), 27.1 (CH_3), 34.1 (CH_2), 39.2 (CH_2), 43.7 (CH), 46.1 (CH), 52.3 (CH), 67.1 (CH_2), 81.5 (CH), 85.7 (CH), 85.9 (C), 104.4 (CH), 113.3 (C), 113.4 (CH_2), 114.9 (CH_2), 119.5 (CH_2), 127.3 (CH), 127.4 (CH), 128.3 (CH), 134.4 (CH), 138.4 (C), 139.8 (CH), 141.9 (CH), 209.0 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{26}H_{32}O_5Na$ 447.2147, found 447.2145. Catalyst **19** (6 mg, 0.007mmol, 2.8 mol %) was then added to the mixture and stirring was continued for 6 h (TLC) under ethylene atmosphere. The solvent was removed under vacuum. The residual mass was purified by column chromatography to afford compound **21a** (86 mg, 86%): $[\alpha]^{24}_D$ −27.5 (*c* 1.5, $CHCl_3$); IR ν_{max} 1726 cm^{-1}; ^1H NMR δ 1.22−1.36 (1H, m), 1.40 (3H, s), 1.60 (3H, s), 1.72−1.76 (1H, m), 1.93−1.97 (1H, m), 2.13−2.19 (1H, m), 2.39−2.49 (1H, m), 3.01−3.11 (1H, m), 3.73−3.79 (1H, m), 4.52 (1H, d, J = 10.3 Hz), 4.59 (1H, d, J = 10.3 Hz), 4.64 (1H, d, J = 3.5 Hz), 4.87 (1H, s), 4.94 (1H, d, J = 10.3 Hz), 5.03 (1H, d, J = 17.1 Hz), 5.52 (1H, dd, J = 3.0, 11.1 Hz), 5.81−5.88 (1H, m), 5.90 (1H, d, J = 3.4 Hz), 6.00 (1H, dd, J = 1.9, 11.0 Hz), 7.33−7.43 (5H, m); ^{13}C NMR δ 27.1 (CH_3), 27.4 (CH_3), 31.3 (CH_2), 39.7 (CH), 43.7 (CH), 43.9 (CH), 46.3 (CH), 67.5 (CH_2), 82.3 (C), 82.9 (CH), 90.2 (CH), 104.6 (CH), 113.8 (C), 113.9 (CH_2), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 138.2 (C), 140.9 (CH), 141.2 (CH), 204.4 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{24}H_{28}O_5Na$ 419.1834, found 419.1836.

Synthesis of the Tricyclic Ketone (23a). Compound **11a** (100 mg, 0.25 mmol) in DCM (50 mL) on treatment with catalyst **18** (15 mg, 0.018 mmol) for 1 h first produced the ring opened product **22a** as revealed by analysis of the spectral data of an aliquot of the reaction mixture: $[\alpha]^{26}_D$ +90.5 (*c* 1.14, $CHCl_3$); IR ν_{max} 1709 cm^{-1}; ^1H NMR δ 1.34 (3H, s), 1.57 (3H, s), 1.73−1.93 (4H, m), 2.40−2.54 (1H, m), 2.88−3.00 (1H, m), 3.51−3.66 (1H, m), 4.61−4.65 (2H, m), 4.76 (1H, d, J = 11.1 Hz), 4.85 (1H, s), 4.93−5.09 (4H, m), 5.29 (1H, d, J = 17.6 Hz), 5.38 (1H, d, J = 11.1 Hz), 5.55−5.67 (2H, m), 5.77−5.88 (1H, m), 5.92 (1H, d, J = 3.3 Hz), 7.31−7.39 (5H, m); ^{13}C NMR δ 27.0 (CH_3), 27.1 (CH_3), 33.6 (CH_2), 39.6 (CH_2), 43.8 (CH), 47.6 (CH), 51.7 (CH), 67.4 (CH_2), 81.5 (CH), 86.2 (C), 87.1 (CH), 104.1 (CH), 113.4 (CH_2), 113.4 (C), 115.9 (CH_2), 118.9 (CH_2), 126.9 (CH), 127.6 (CH), 128.4 (CH), 133.6 (CH), 138.4 (C), 139.2 (CH), 141.8 (CH), 206.1 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{26}H_{32}O_5Na$ 447.2148, found 447.2146. Continuation of the reaction on addition of catalyst **19** (12 mg, 0.014 mmol) in the same pot for 10 h afforded after chromatographic purification the tricyclic compound **23a** (80 mg, 80%): $[\alpha]^{24}_D$ +40.4 (*c* 2.6, $CHCl_3$); IR ν_{max} 1714 cm^{-1}; ^1H NMR δ 1.14−1.25 (1H, m), 1.31 (3H, s), 1.54 (3H, s), 1.78−1.84 (2H, m), 2.14−2.23 (1H, m), 2.35−2.45 (1H, m), 3.16−3.20 (1H, m), 3.53−3.58 (1H, m), 4.35 (1H, d, J = 3.0 Hz), 4.47 (1H, d, J = 11.6 Hz), 4.68 (1H, d, J = 11.7 Hz), 4.77 (1H, s), 4.88 (1H, d, J = 10.2 Hz), 4.99 (1H, d, J = 17.1 Hz), 5.35 (1H, dd, J = 2.1, 12.9 Hz), 5.68−5.79 (3H, m), 7.17−7.29 (5H, m); ^{13}C NMR δ 27.0 (CH_3), 27.5 (CH_3), 32.7 (CH_2), 38.6 (CH), 41.9 (CH), 42.6 (CH_2), 52.9 (CH), 67.7 (CH_2), 84.3 (C), 84.9 (CH), 85.4 (CH), 104.3 (CH), 114.0 (CH), 114.4 (C), 125.3 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 138.7 (C), 139.1 (CH), 141.2 (CH), 208.7 (CO); HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{24}H_{28}O_5Na$ 419.1834, found 419.1833.

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Supporting Information Available: General methods and procedures along with spectral data for compounds **4a**−**e**, **5b**−**e**, **6b**−**e**, **7**, **8**, **9**, **10b**−**d**, **11b**−**d**, **15**, **16**, and **17**, **21b**−**d**, **23b**−**d**, **24**, and **25** and X-ray crystal data with ORTEP plot for compound **10d**, copies of ^{1}H and ^{13}C NMR spectra of compounds **4a**−**e**, **5a**−**e**, **6a**−**e**, **7**, **8**, **9**, **10a**−**d**, **11a**−**d**, **15**, **16**, and **17**, **20a**,**b**,**d**, **21a**−**d**, **22a**,**c**,**d**, **23a**−**d**, **24**, and **25** and copies of NOESY spectra of compounds **21a** and **23a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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