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Remarkable stereocontrol in the synthesis of 1,2,3,5-tetrasubstituted tetrahydropyrans via an asymmetric heterocycloaddition of a ketone-derived enol ether

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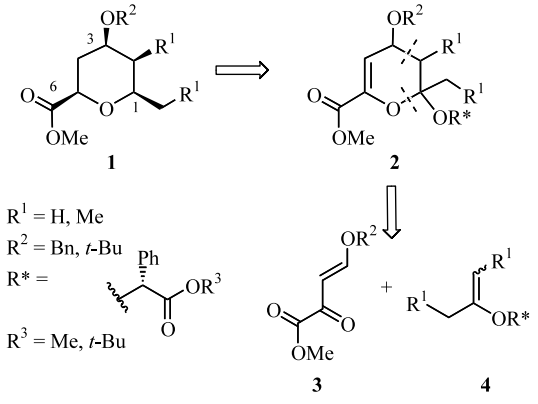
Abstract—The synthesis of chiral 1,2,3,5-substituted tetrahydropyrans has been realized via an asymmetric hetero Diels–Alder (HDA) reaction. The key step that involved a trisubstituted chiral enol ether derived from (*R*)-mandelic acid as the dienophile promoted the creation of three stereogenic centers with a remarkable and unprecedented *endo* and facial stereocontrol. The hydrogenation of the heteroadduct **2** was optimized by using Pd on charcoal and diisopropylethylamine, leading to a unique isomer. The chiral inductor was cleanly and stereoselectively removed via an acetal reduction, which demonstrated the potential of this methodology for the efficient construction of key intermediate of biologically active molecules.

Carba-analogues of glycosides have attracted considerable interest over the last three decades in view of their hydrolytic stability and potential enzyme inhibitory properties.[1] Moreover, *C*-glycosides have proven to be exceedingly useful building blocks for the synthesis of natural products with important pharmacological properties, which has stimulated the development of new synthetic methodologies.[2] During the course of our synthetic studies toward ambruticin,[3] a fascinating antibiotic[4] which came back in the front scene with three recent total syntheses,[5] we have been interested in the synthesis of chiral tetrahydropyrans. Moreover, 1,2,5-trialkyl-3-hydroxy-tetrahydropyrans constitute important key intermediates for other molecules such as lasonolide A,[6] polycavernoside A,[7] ratjadone,[8] or concanamycin A.[9]

We turned our attention to the preparation of (*L*)-2,4-dideoxy-*C*-glycoside derivatives and wish to describe a novel approach to chiral ester **1**, from which diverse functionalizations could be introduced at carbon C-6 (Scheme 1). The tetrasubstituted tetrahydropyran **1** could result from heteroadduct **2**, via a stereoselective hydrogenation of the double bond and reduction at carbon C-1. The dihydropyran **2** was expected to be stereoselectively and asymmetrically delivered by means of an inverse-electron demand hetero Diels–Alder (HDA) reaction[10] between the activated heterodiene **3** and the enol ether **4**.



Scheme 1. Retrosynthesis.

Keywords: asymmetric hetero Diels–Alder; chiral *C*-glycosides; stereocontrolled hydrogenation; acetal reduction; ketone-derived enol ether.

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The key [4+2] heterocycloaddition was particularly tricky as it involved a trisubstituted dienophile. Indeed, despite the tremendous recent progress achieved in the area of HDA reactions with the use of Cu^{II} and Cr^{III}-based asymmetric catalysis,[10e,11] the simultaneous control of *endo*/*exo* and facial selectivity remains a difficult challenge when the dienophile is a dialkyl ketone-derived enol ether. Considering our previous results and expertise concerning the $Eu(fod)_3$-catalyzed heterocycloaddition of vinyl chiral ethers,[12] we chose to investigate enol ethers derived from (*R*)-mandelic acid as chiral dienophiles. The preparation of the heterodienes **3a**–**b** (Fig. 1) was based on previous methodology.[12b] A model study involving **3a** towards various *O*-isopropenyl mandelic esters[13] (**4a**-type) as the dienophile, under typical $Eu(fod)_3$-catalyzed conditions led to the expected adducts in good yields with a high level of *endo* control. However, the major *endo* adducts were obtained with a moderate diastereofacial selectivity, which confirmed some previously disclosed observations.[11e]

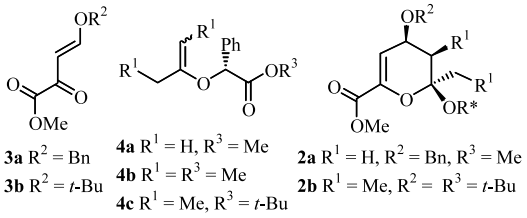
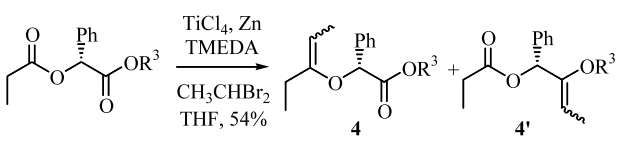


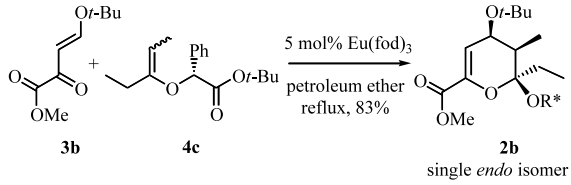
Figure 1.

The preparation of chiral enol ethers derived from 3-pentanone ($R^1 = Me$) was thus investigated. Application of our previous method involving regiocontrolled elimination of a mixed acetal with TMSOTf and triethylamine[13] gave poor results. Access to **4**-type compounds was envisaged via a regiocontrolled ethylidenation, namely a Takai reaction[14] of the corresponding diester **5** (Scheme 2). Firstly applied to the methyl ester **5a**, the Takai reaction using $Zn/TiCl_4$ reagents and 1,1-dibromoethane proved to be non-selective: enol ether **4b** and its regioisomer **4′b** were produced in a 4/1 ratio. In contrast, the same conditions applied to the bulkier *t*-butyl ester **5b** gave rise to the desired enol ether **4c** with a total regiocontrol. Alkene **4c** was isolated in 54% yield as a 9/1 *Z*/*E* mixture identified by ^1H NMR NOe measurements. The two stereoisomers could be separated by careful chromatography on silica gel, but the mixture was engaged directly in the next step.



Scheme 2. Synthesis of enol ethers **4**.

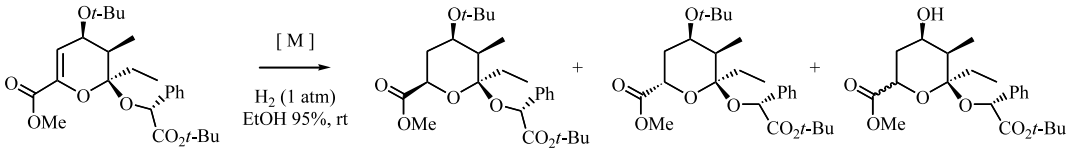
The key heterocycloaddition was thus investigated under $Eu(fod)_3$-catalyzed conditions. It was found that reaction of enol ether **4c** with heterodiene **3b** in the presence of 5 mol% $Eu(fod)_3$ in refluxing petroleum ether was particularly effective and led to the functionalized dihydropyran **2b** with 83% yield (Scheme 3). Moreover, we were pleased to find that **2b** was isolated as a single *endo* isomer:[15] the major *Z* isomer of **4c** thus underwent a very clean *endo*-selective and asymmetric HDA reaction, meanwhile its *E* isomer was recovered unchanged after the reaction. The lack of reactivity of the *E* isomer of **4c** with **3b** could be explained by severe steric interaction in the $Eu(fod)_3$-chelated, favored, *endo*-transition state. This fact agrees with previous findings concerning the $Eu(fod)_3$-catalyzed heterocycloaddition of cyclanone-derived enol ethers when using the same heterodiene.[16] To our knowledge, the obtention of adduct **2b** as a sole diastereomer affords an unprecedented example of total *endo* and asymmetric control in an inverse-electron demand HDA reaction involving a dialkylketone-derived enol ether as the dienophile.



Scheme 3. [4+2] Heterocycloaddition.

The catalytic hydrogenation was then studied and proved to be very difficult. The formation of compound **6** was expected as it is well established that the addition of hydrogen generally occurs on the less hindered face of the alkenes. Nevertheless, even though many 1,3,5-substituted dihydropyrans were stereoselectively hydrogenated using 10% palladium on activated charcoal under 1–3 bar hydrogen pressure,[17,18] no relevant examples were described starting from 1,1′,2,3,5-substituted dihydropyrans. As shown in Table 1 (entry 1), the above mentioned conditions proved to be non selective and gave a mixture of tetrahydropyrans **6**, ***epi*-6** and alcohol **7**.[19,20] The use of Pd 5% on carbon under one atmosphere of hydrogen, in 95% aqueous ethanol, at room temperature (entry 2) also afforded a complex mixture, in which the major adduct was the deprotected 3-hydroxy compound **7**. Higher catalyst loading (entry 3) shortened the reaction time but did not give better results. In contrast, the use of 50% wet palladium on carbon restricted to 5% the deprotection ratio and led to pure crystallized tetrahydropyran **6** in moderate isolated yield (entry 4). X-Ray analysis of compound **6** proved the overall *syn* relationship of OR* at C-1, Me at C-2, O*t*-Bu at C-3 and CO_2Me at C-5. The relationship between inducing and induced stereogenic centers definitively established the absolute configuration of **6** (and **2b**, Scheme 3). Further experiments were performed to enhance the selectivity in the formation of **6**.

Table 1. Hydrogenation of dihydropyran **2b**



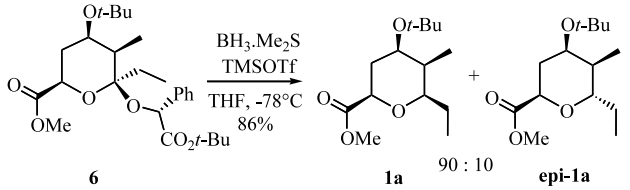
2b **6** **epi-6** **7**

Entry	Catalyst (% weight)	*t* (h)	Isomer ratio (%)[a] **6**/***epi*-6**/**7**	Overall conversion/**2b** (isolated yield of **6**)
1	Pd 10% on C (10)[b]	3	50:25:25	100
2	Pd 5% on C (10)	21	37:13:50	100
3	Pd 5% on C (15)	5	17:16:67	100
4	wet Pd 5% on C (25)	15	76:19:5	100 (56)
5	PtO_2 (10)	44	100:0:0	20
6	Pd 5% on C (15), *i*-Pr_2NEt (15)	5	100:0:0	100 (83)

[a] Measured by ^1H NMR, based on the benzylic proton of the mandelic ester moiety (Ref. 19).
[b] 3 bar.

The use of PtO_2[18] as the catalyst (entry 5) afforded a clean hydrogenation with a high selectivity despite 80% of starting material being recovered. Meanwhile, suspecting that the formation of **7** was due to catalyst acidity, we added 15% weight of diisopropylethylamine.[18c] We were grateful to find that the Pd-catalyzed hydrogenation was much cleaner, faster and led to the unique isomer **6** in 83% isolated yield (entry 6). Moreover, the reaction could be scaled up to 1.4 g of substrate **2b**.[21]

The next crucial step consisted in the reduction of the acetal **6**. We had envisaged the cleavage of the chiral inductor to form the lactol followed by a Kishi reaction[22] which proved particularly efficient for the preparation[23] of *C*-glycosides. The selective reduction of simple ketals using $BH_3{\cdot}Me_2S$/TMSOTf, described by Bartels et al. drew our attention.[24] We were grateful to find that it could be applied in target-oriented synthesis.



6 **1a** **epi-1a**

Scheme 4. Ketal reduction of tetrahydropyran **6**.

Indeed, reduction of ketal **6** provided a mixture of **1a**[25] and ***epi*-1a** in an optimized 90/10 ratio with 86% yield (Scheme 4). Each epimer could be isolated by chromatography on silica gel. The relative and then absolute stereochemistry of the newly created center of pyrans **1a** and ***epi*-1a** was confirmed by ^1H NMR NOE measurements.

In conclusion we have disclosed a highly stereocontrolled three-step sequence for the efficient asymmetric access to 1,2,3,5-substituted tetrahydropyrans. The key step, that involved the $Eu(fod)_3$-catalyzed HDA reaction of a trisubstituted chiral enol ether derived from (*R*)-mandelic acid and an activated heterodiene, promoted the creation of three stereogenic centers with unprecedented *endo* and facial controls. Stereoselective hydrogenation of the 1-alkoxydihydropyran thus obtained was optimized by using Pd on charcoal and diisopropylethylamine. The subsequent acetal reduction, performed with $BH_3{\cdot}Me_2S$/TMSOTf, achieved to demonstrate the potential of this approach for the ready construction of complex tetrahydropyranic intermediates for biologically active molecules. Further studies are directed at exploring new applications of this methodology toward the total synthesis of natural products and analogues.

Acknowledgements

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19. All isomeric ratios indicated in this work were determined by ^{1}H NMR (400 MHz) on the crude material. For each hydrogenation assay (Table 1), the evaluation of the **6**/*epi*-**6**/**7** ratio was based on the integration of the benzylic proton of the mandelic ester moiety: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (**6**), 5.26 (*epi*-**6**), 5.14 (**7**) ppm. The relative stereochemistry of alcohol **7** was not established.
20. A lack of selectivity was recently observed in the catalytic hydrogenation of bicyclic 1,1′,2,3,5-substituted dihydropyrans: Martel, A.; Dujardin, G.; Brown, E. *Synthesis* **2003**, in press.
21. Tetrahydropyran **6**: Mp = 150–152°C; $[\alpha]_D^{20}$ −2.8 (*c* 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 2H), 7.28 (m, 3H), 5.46 (s, 1H), 4.19 (dd, J = 11.2, 4.0 Hz, 1H), 3.79 (ddd, J = 10.2, 5.1, 5.1 Hz, 1H), 3.51 (s, 3H), 2.12 (qd, J = 6.8, 5.1 Hz, 1H), 1.74 (m, 2H), 1.89 (m, 2H), 1.39 (s, 9H), 1.19 (s, 9H), 0.99 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 138.3, 127.8, 127.3, 127.0, 104.3, 80.9, 73.6, 72.3, 69.9, 65.8, 51.8, 38.4, 31.5, 28.3, 27.8, 26.4, 8.4, 8.3; Microanalysis: calcd for $C_{26}H_{40}O_7$: C, 67.22 H, 8.68, Found: C, 67.45 H, 8.73.
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25. Tetrahydropyran **1a**: $[\alpha]_D^{20}$ +39.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (dd, J = 12.0, 2.8 Hz, 1H), 3.76 (s, 3H), 3.68 (dt, J = 11.4, 4.9 Hz, 1H), 3.27 (ddd, J = 7.7, 6.1, 1.8 Hz, 1H), 1.85–1.65 (m, 4H), 1.50–1.40 (m, 1H), 1.20 (s, 9H), 0.91 (t, J = 7.5 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.3, 81.2, 75.5, 73.6, 70.0, 52.0, 37.8, 32.0, 28.4, 25.3, 10.2, 5.1. HRMS-DCI/CH_4: $[M+H]^+$ calcd for $C_{14}H_{27}O_4$: 259.1909, found: 259.1915.