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High-Pressure Hetero-Diels−Alder Route to (±)-6,6,6-Trifluoro-β-*C*-Naphthyl Glycosides

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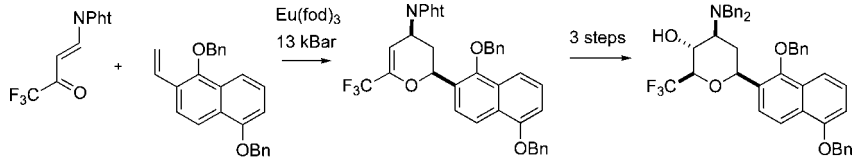
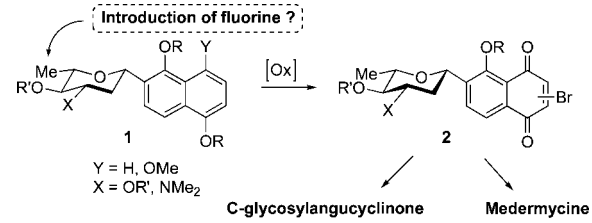
ABSTRACT



The first de novo synthesis of a β-*C*-naphthyl glycoside displaying a convenient functionality for subsequent transformations into complex *C*-aryl glycosides is reported. The synthesis of this (±)-β-*C*-1,5-dibenzyloxynaphthyl 6,6,6-trifluoro-3-amino glycoside relies on a hyperbaric HDA reaction involving a new 2-vinylnaphthalenic dienophile.

β-*C*-Naphthyl-2-deoxy glycosides **1** are pivotal precursors of natural *C*-aryl glycosides such as angucyclines[1] and medermycines[2] as a result of their ability to afford the corresponding bromojuglone **2**, which acts as dienophile in the formation of the key B ring (Scheme 1). The importance of naphthyl glycosides **1** has stimulated much effort for their synthesis[3] by classical C-glycosylation,[4] organometallic condensation,[1a,b] or construction of the naphthalene ring from a *C*-glycosylfuran.[5]

Scheme 1. Proposed Route to Modified β-*C*-Aryl Glycosides



The introduction of fluorine (1−3 F atoms) at the C-6 position of *C*-naphthyl glycosides is a challenging task, likely to provide analogues of biological interest. However, altering the sugar unit after C-glycosylation is quite difficult.[6] The

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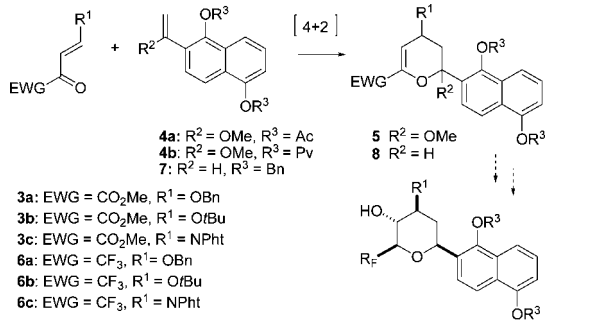
elaboration of 6-fluorinated glycosyl donors for subsequent C-glycosylation has been investigated in the literature[7] and by our group.[8] However, 6,6,6-trifluoro-olivosyl donors are inefficient for the *C*-glycosylation of 1,5-dihydroxynaphthalene[8] or its derivatives.[7]

We therefore investigated an alternative [4 + 2] route toward *C*-naphthyl glycosides based on a $SnCl_4$-catalyzed heterocycloaddition between an α-methoxyvinylnaphthalene and a "prosugar" heterodiene[9] bearing an activating ester group at the pivotal pro-C-6 position. We also described the access to *β*-*C*-naphthyl glycosides from the resulting dihydropyran via a new hydroboration/reduction/oxidation tandem reaction (HyBRedOx).[10] This method allows the introduction of one or two fluorine atoms at the C-6 position prior to the HyBRredOx sequence.[10a] This strategy efficiently provided type-5 heteroadducts from ketone enol ether dienophiles **4** displaying a 1,5-dihydroxynaphthalene moiety and heterodienes **3** (Scheme 2) but failed to transform these

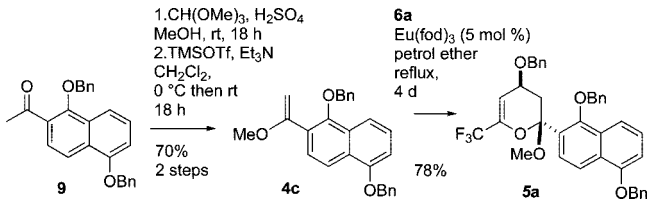
Scheme 2. [4 + 2] Route to *C*-Naphthyl Glycosides



heteroadducts into the desired precursors of *C*-glycosyl bromojuglones.[11] In this paper, we report the first access to a (±)-6,6,6-trifluoro-*β*-*C*-naphthyl glycoside via high pressure $Eu(fod)_3$-catalyzed hetero-Diels−Alder (HDA) reaction of heterodiene **6** with a new dienophile, the 2-vinyl-1,5-dibenzyloxynaphthalene **7**.

Our first attempts to access 6,6,6-trifluoro-*C*-naphthyl glycoside (Scheme 2, EWG = R_F = CF_3) focused on type-**5** adducts (R^2 = OMe). From oxadienes **6** and activated dienophiles **4**, the reaction did not proceed under $SnCl_4$-catalyzed conditions. In contrast, $Eu(fod)_3$-catalyzed reaction between **6a** and **4c** led to the *endo* adduct **5a** in good yield (Scheme 3).

Scheme 3. Stereocontrolled Access to Adduct **5a**

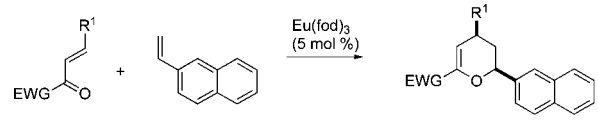


Unfortunately, as in the ester series, we were unable to transform adduct **5a** into the corresponding glycoside.[8]

In this context, we reinvestigated the more direct [4 + 2] approach involving less reactive vinylnaphthalene derivatives as dienophiles. Access to *C*-naphthyl glycosides could then result from a simple hydroboration-oxidation applied to the type-**8** adduct (after prior reduction in the ester series). The desired *cis* configuration requires an *endo*-selective cycloaddition, which could in turn result from appropriate conditions.

In the ester series, we had found previously that an unactivated dienophile such as 2-vinylnaphthalene was inert toward "prosugar" heterodienes **3a,b** (Table 1, entries 1 and

Table 1. HDA Reactions of 2-Vinylnaphthalenes: Model Study



3a: EWG = CO_2Me, R^1 = OBn
3b: EWG = CO_2Me, R^1 = O*t*Bu
3c: EWG = CO_2Me, R^1 = NPht
6a: EWG = CF_3, R^1= OBn
6b: EWG = CF_3, R^1 = O*t*Bu
6c: EWG = CF_3, R^1 = NPht

10: EWG = CO_2Me, R^1 = NPht
11: EWG = CF_3, R^1 = NPht

entry	diene	conditions[a]	adduct	yield (%)[b]	dr[c]
1	**3a**	A		0	
2	**3b**	A		0	
3	**6a**	A		0	
4	**6b**	A		0	
5	**3c**	A	**10**	70	>97/3
6	**6c**	A		0	
7	**6c**	B	**11**	76	>97/3

[a] Conditions A: CH_2Cl_2, 42 °C, 5 days. Conditions B: toluene, 110 °C, 12 days. [b] Isolated products. [c] Determined by ^1H NMR analysis.

2).[9a] Expectedly, a similar behavior was observed toward trifluoromethylated analogues **6a,b**[12] (entries 3 and 4). In contrast, we were pleased to discover that the $Eu(fod)_3$-catalyzed HDA reaction can occur *endo*-selectively under mild thermal conditions when starting from the 4-*N*-phthalimido-substituted heterodiene **3c** (entry 5). The higher reactivity of *N*-Pht heterodiene **3c**, when compared to *O*-alkylated ones, could result from more favorable geometric factors in the *endo* TS, as previously suggested in the case of arylidene pyruvic acid esters.[9a] Under the same conditions, trifluoromethylated *N*-Pht-heterodiene **6c** did not react (entry 6). However, prolonging the reaction time at higher tem-

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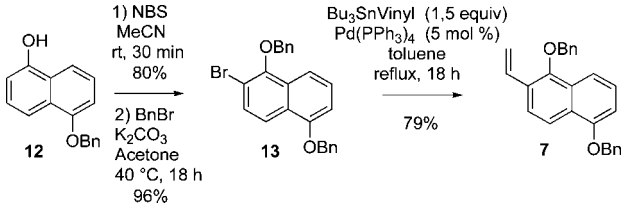
perature (refluxing toluene) led to adduct **11**, isolated in 76% yield in a high *endo*-selectivity (entry 7).

Encouraged by these results, we investigated the synthesis of a vinylnaphthalene that could afford juglone precursors: the 2-vinyl-1,5-dibenzyloxynaphthalene **7** (Scheme 4). This

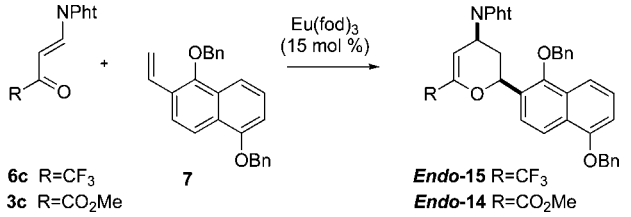
Scheme 4. Synthesis of Dienophile **7**



new potent dienophile was prepared in three steps from the monobenzylated 1,5-dihydroxynaphthalene via ortho-bromination, O-protection, and Stille coupling with tributylvinylstannane. The use of NBS in the first step prevented dibromination in the *ortho*/*para* phenolic positions.[1a,b]

Eu(fod)$_3$-catalyzed HDA reactions between dienes **3c** or **6c** and dienophile **7** were attempted under the thermal conditions initially used with 2-vinylnaphthalene (Table 2).

Table 2. HDA Reactions of Dienophile **7**



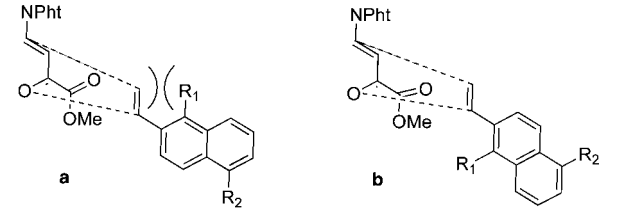
entry	diene	conditions	adduct	yield (%)[a]
1	**3c**	toluene, 110 °C, 12 d		0
2	**6c**	toluene, 110 °C, 12 d		0
3	**3c**	toluene, MW, 170 °C, 0.5 h		0
4	**6c**	toluene, MW, 170 °C, 0.5 h		0
5	**6c**	CH_2Cl_2, 13 kbar, 50 °C, 4 d[b]		0
6	**3c**	CH_2Cl_2, 13 kbar, 50 °C, 1 d	**14**	25
7	**6c**	CH_2Cl_2, 13 kbar, 50 °C, 1 d	**15**	15
8	**3c**	CH_2Cl_2, 13 kbar, 50 °C, 4 d	**14**	44[c] (74)[d]
9	**6c**	CH_2Cl_2, 13 kbar, 50 °C, 4 d	**15**	50[c] (88)[d]

[a] Purified product. [b] No Eu(fod)$_3$ catalyst was used in this case. [c] dr >97/3. [d] Yield based on recovered starting material.

No reaction occurred, even when the reaction time was prolonged or the temperature increased (entries 1 and 2). Microwave irradiation was also ineffective (entries 3 and 4). Whatever conditions were used, usually only starting material was recovered.

The difference in reactivity between 2-vinylnaphthalene and its dibenzyloxy analogue **7** was quite unexpected. In order to check the causes of this lack of reactivity, the transition states involving the vinylnaphthalene and its dibenzyloxy analogue were analyzed by DFT calculations at the B3LYP/6-31G(d) level. The transition states involving the monobenzyloxynaphthalene were also determined in order to compare the steric and the electronic effect of the benzyloxy group close to the reacting center. The computed activation parameters in the gas phase at 50 °C are given in Table 3.

Table 3. Gas-Phase Activation Parameters (kcal/mol) at 323 K Computed from the *endo* TS-(**10**,**14**,**16**)-**a**,**b** at the B3LYP/6-31G(d) Level of Theory



		TS-**10** ($R^1 = R^2 = H$)		TS-**16** (R^1 = OBn, $R^2 = H$)		TS-**14** ($R^1 = R^2$ = OBn)	
entry		**a**	**b**	**a**	**b**	**a**	**b**
1	$\Delta E^{\ddagger}$	20.0	21.5	25.6	20.6	27.0	21.4
2	$\Delta G^{\ddagger}_{323}$	35.6	36.9	40.8	35.7	43.6	36.9
3	$\Delta H^{\ddagger}_{323}$	19.5	21.0	25.3	20.3	26.4	21.0

The geometry of the TS proved that the course of the reaction is significantly asynchronous as illustrated by Table 4. As is generally observed with similar push−pull dienes,

Table 4. Bond Lengths (Å) of the Bond Formed at the TS

entry	TS	C−C	C−O
1	**10b**	1958	2414
2	**16b**	1966	2338
3	**14b**	1968	2333

the C−C bond is formed slightly prior to the C−O bond. The reaction is therefore mainly controlled by the ability of the system to stabilize the partial charges.

TS **a** is disfavored in the case of TS-**16** and TS-**14** as a result of the steric hindrance caused by R^1 substituent (Table 3). This rotation of the vinyl group in the conformation adopted by the dienophile in the TS could give a first explanation for the lack of reactivity observed and could be related to the position of the catalyst in the TS. A constant growth of the activation energy ($\Delta E^{\ddagger}$) is observed from TS-**10a** to TS-**16b** and -**14b**, whereas the free Gibbs energies

(13) The experimental conditions (Lewis acid catalysis and pressure), which are not taken into account in these calculations, may have a significant influence on the course of the cycloaddition process.

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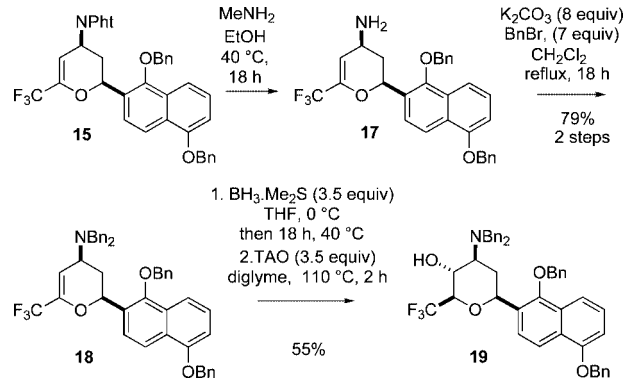
of TS-**10a** and TS-**16b** at 323 K are similar, within the error of the calculations. The expected free Gibbs energy gap is only observed for TS-**14b** (1.2 kcal/mol).[13] This indicates that the lack of reactivity of dienophile **7** is mainly due to electronic effects and not to the steric hindrance caused by the presence of the benzyloxy group.

Research from past decades has shown that pressure in the range of 1−20 kbar strongly influences the rate of processes accompanied by a decrease in volume. The highly negative activation volume (typically −23 to −51 $cm^3 \cdot mol^{-1}$) characterizing Diels−Alder cycloadditions has generated many studies that unambiguously demonstrate a powerful pressure-induced acceleration of these reactions.[14] Increase in *endo* selectivity is generally observed under these operating conditions.[15] Synergistic effects of Lewis acid catalysis and high pressures have also been observed.[16] Interestingly, Schmidt's group demonstrated the efficiency of hyperbaric conditions (6.2 kbar) on HDA reactions involving styrenes.[9b] Scheeren and co-workers evidenced the synergistic effects of Eu(fod)$_3$-catalysis and high pressure conditions in the formation of dihydropyrans from vinyl ethers.[17]

Compressing heterodiene **6c** with **7** to 13 kbar in the absence of any Lewis acid, however, was not sufficient to promote the cycloaddition in our case (Table 2, entry 5). In contrast, activation by Lewis acid and 13 kbar pressure at 50 °C showed the positive impact of the multiactivated process and allowed the formation of the *cis*-adducts **14** and **15**, in a complete *endo*-selective manner (entries 6 and 7). However, the isolated yields were low. Increasing reaction time to 4 days under otherwise identical conditions ensured good conversions and enhanced yields of 44% and 50%, respectively (entries 8 and 9). Under these conditions, residual dienophile **7** could be recovered and yields based on unrecovered starting material were good (74% and 88%, respectively).

From these new and promising [4 + 2] adducts obtained with a high *cis*-selectivity, we first investigated access to the corresponding *β-C*-naphthyl glycosides in the trifluoromethyl series (Scheme 5). N-Deprotection of adduct **15** was conveniently conducted under mild aminolysis conditions by treatment with an ethanolic solution of methylamine at 40 °C. Subsequent dibenzylation of the crude primary amine[18] afforded the tetrabenzylated derivative **18** in good overall yields. Hydroboration of **18** was conducted with $BH_3 \cdot Me_2S$ complex at 40 °C in THF. After 24 h and

Scheme 5. Synthesis of (±)-Trifluoro-*β-C*-naphthyl Glycoside **19**



subsequent treatment of the borane by trimethylamine *N*-oxide in diglyme,[19] ^{1}H NMR of the crude product showed the total disappearance of the vinylic proton. After purification on silicagel, the pure *C*-naphthyl glycoside (±)-**19** was obtained in 55% yield with a complete diastereocontrol.

To conclude, the present work exemplifies the first successful de novo access to a *rac-β-C*-naphthyl-2-deoxy glycoside that can act as a *C*-glycosylbromojuglone precursor. The key step of this synthesis is a high pressure/Eu(fod)$_3$-catalyzed HDA reaction between an activated heterodiene (that delivers both amino and trifluoromethyl groups in the final glycoside) and a new dienophile, the 2-vinyl-1,5-dibenzyloxynaphthalene (**7**). The *β-C*-naphthyl-6,6,6-trifluoro-3-amino glycoside described herein provides a fine illustration of the regiocontrolled introduction of fluorine and nitrogen atoms that can be carried out on the glycoside moiety by this strategy. The generalization of this approach to other modifications of the glycoside unit (e.g., mono- or bis-fluorination at the C-6 position via the adduct **14**), and its asymmetric extension is under progress in our laboratories.

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Supporting Information Available: Experimental procedures and spectroscopic data for synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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