DOI: 10.1002/ejoc.200800655

[4+2]/HyBRedOx Approach to *C*-Naphthyl Glycosides: Failure in the Projuglone Series and Reinvestigation of the HyBRedOx Sequence

Lucie Maingot,[a,b] Nguyen Quang Vu,[a] Sylvain Collet,[b] André Guingant,[b] Arnaud Martel,[a] and Gilles Dujardin*[a]

Keywords: Tin / Cycloaddition / Dienophiles / Glycosides / Heterocycles

C-Naphthyl glycosides displaying a 1,5-difunctionality on the naphthalene ring that can undergo oxidation to bromonaphthoquinone are key intermediates in the synthesis of natural *C*-aryl glycoside analogues. In this area, sugar-modified derivatives are of specific interest, but their synthesis is challenging. The de novo access to such compounds has been investigated through a [4+2] heterocycloaddition route, previously validated in a model series. For this purpose, two new dienophiles, conveniently protected at the phenolic positions, were synthesized. From an extensive study of their reactivity towards a range of 4-hetero-substituted ("pro-sugar") heterodienes, the expected heteroadducts were stereoselectively obtained in acceptable yields. Application of the hydroboration/reduction/oxidation sequence did not afford the target *C*-glycosides from the reduced adducts. The negative effect of the conformational bias of the substrate on this tandem reaction is discussed.

Introduction

C-Naphthyl-2-deoxy glycosides **1** are pivotal precursors for the synthesis of several classes of natural *C*-aryl glycosides (Figure 1), for example, angucyclines[1] and medermycines.[2] In these approaches, 1,5-oxy disubstitution of the naphthalene ring is convenient for delivering the corresponding bromojuglone **2** subsequently involved in the key formation of the B ring. The importance of *C*-naphthyl-2-deoxy glycosides **1** has stimulated much effort towards their synthesis[3] by classical *C*-glycosylation[4] or organometallic condensation.[1a,1b] The limitations of these methods led to the development of new strategies involving the construction of the naphthalene ring from a *C*-glycosylfuran.[5]

In the development of biologically active analogues, sugar-modified derivatives of *C*-naphthyl glycosides **1** are of interest. Owing to the polyfunctionality of **1**, modifications of the sugar unit after *C*-glycosylation are restricted.[6] An approach involving modification of glycosyl donors prior to *C*-glycosylation has also been reported in the literature, but failed in some critical cases.[7] De novo approaches involving the construction of the glycosyl ring have seldom been reported.[8,9]

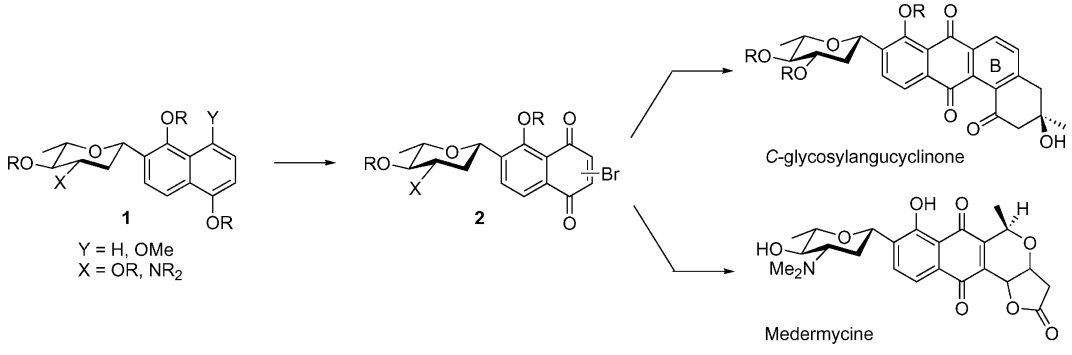

Figure 1. *C*-Naphthyl glycosides as key intermediates of biologically active complex *C*-aryl glycosides.

[a] UCO2M, UMR CNRS 6011, Universite du Maine, 72085 Le Mans Cedex 9, France
Fax: +33-2-43833902
E-mail: gilles.dujardin@univ-lemans.fr
[b] CEISAM, UMR CNRS 6230, Universite de Nantes, UFR Sciences et Techniques, 2 rue de la Houssiniere, B. P. 92208, 44322 Nantes Cedex, France

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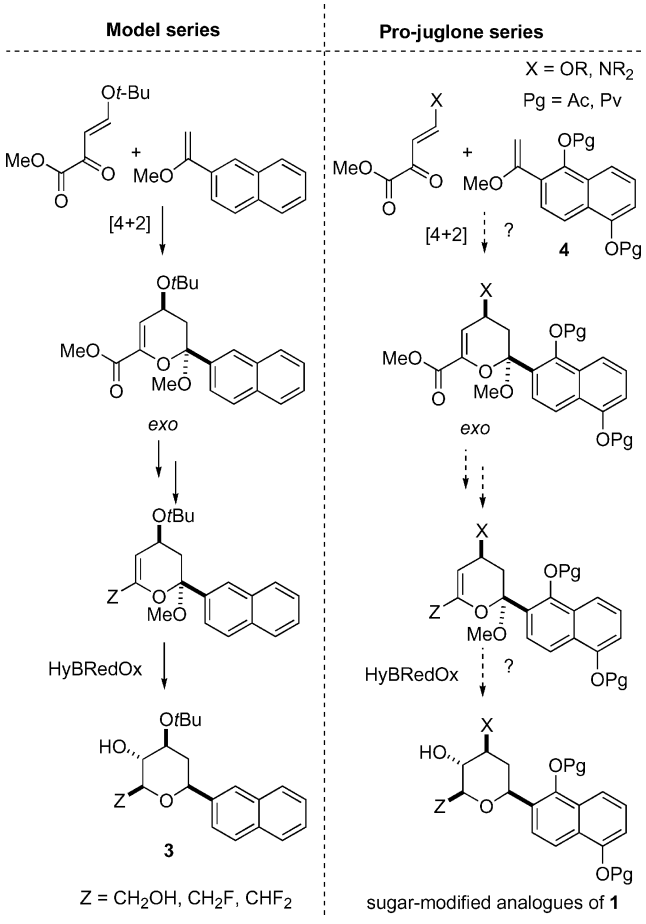
Inspired by the pioneering work of Schmidt et al.,[10] we investigated a [4+2] route towards *C*-naphthyl glycosides (Scheme 1, the model series) by a $SnCl_4$-catalyzed heterocycloaddition of α-methoxyvinylnaphthalene with a "pro-sugar" heterodiene.[11] In a previous report we described the access to β-*C*-naphthyl glycosides **3** from the reduced dihydropyran obtained by an unprecedented hydroboration/reduction/oxidation tandem reaction (HyBRedOx) using the BH_3·THF complex as the hydroborating/ketal-reducing agent.[12] The efficiency of this one-pot sequence was found to be highly dependent on the configuration of the substrate because derivatives of *endo* adducts proved to be less or nonreactive. Having validated a stereoselective access to β-*C*-glycosides by this [4+2]/HyBRedOx route, we have focused more recently on the application of this strategy to the de novo synthesis of *C*-glycosyl bromojuglones. This required the use of dienophiles **4**, which display a 1,5-dihydroxynaphthalene moiety. In this paper we describe the synthesis of such novel polyfunctionalized dienophiles (Pg = Ac, Pv) and the study of their reactivity with different "pro-sugar" heterodienes (X = OR, NR_2). In the second part, the application of the HyBRedOx sequence and its failure are discussed.



Scheme 1. De novo approach to *C*-naphthyl glycosides.

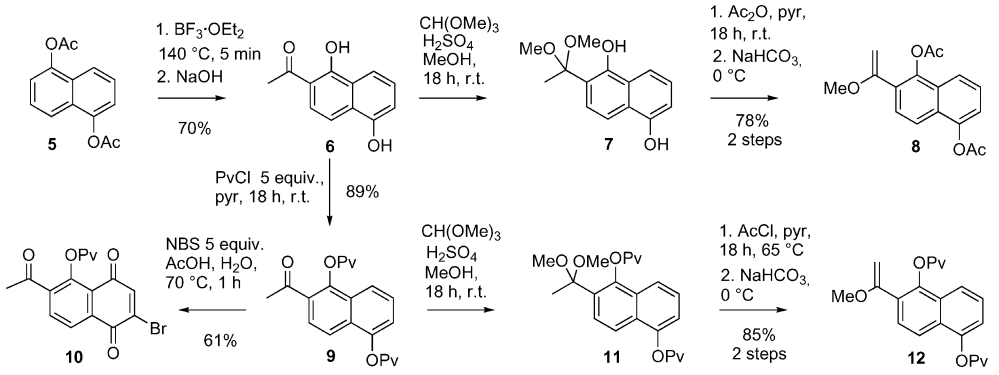
Results and Discussion

Preparation of the Dienophiles

The naphthalene ring must be suitably 1,5-difunctionalized in a diprotected form to give access to bromojuglones by Grunwell oxidation[13] at a late stage. To equip the dienophile, this double *O*-protection had to be compatible with the conditions of the heterocycloaddition reaction: The use of $SnCl_4$ as catalyst thus excluded acid-sensitive protections such as MOM or benzyl. The choice of acetate protection appeared as the most suitable on account of the well-known ability of 1,5-diacetoxynaphthalene to undergo Grunwell oxidation to bromonaphthoquinone.[13] However, with this type of protection we could predict some difficulties relating to the transformation of the heteroadduct into the *C*-glycosyl unit as both the ester reduction of the adduct and the oxidation of borane at the HyBRedOx stage could not be easily conducted in a chemoselective way. For this reason the pivalate group (Pv) was also considered as an alternative ester-type phenol protection as it is more stable under basic and reducing conditions than the acetate group. Moreover, we could expect such protections to be fairly stable under the conditions of [4+2] activation with $SnCl_4$. In addition, we had to check the ability of the pivaloyl protecting groups to allow Grunwell oxidation. For this purpose, the bis-pivalate **9**, easily prepared from **6**, was treated with 5 equiv. of NBS in aqueous acetic acid at 70 °C and led to the expected bromonaphthoquinone **10** in acceptable yields. This result validates the choice of pivalate as an alternative to acetate protection and thus supported our plan to prepare the two dienophiles **8** and **12** (Scheme 2).

The diacetylated dienophile **8** was obtained in three steps starting from 1,5-diacetoxynaphthalene (**5**). The first step was the Fries rearrangement described by Uno.[14] 1,5-Diacetoxynaphthalene (**5**) was subjected to solvent-free thermal reaction with BF_3·OEt_2 followed by saponification of the residual monoacetate to give ketone **6** with total ortho regioselectivity in 70% overall yield. The latter was then treated with methyl orthoformate in an acidic medium to give the naphthalenediol ketal **7**. When submitted to classical acetylation conditions (acetic anhydride/pyridine), ketal **7** underwent concomitant dehydromethoxylation to give the desired diacetylated enol ether **8** directly. In this one-pot process, methanol is efficiently trapped by an excess of acetic anhydride.

Attempts to prepare the corresponding bis-pivalate **12** by treatment of ketal **7** with pivaloyl chloride in pyridine were unsuccessful. However, introduction of pivaloyl protection at an early stage proved to be convenient. Indeed, the bis-pivaloyloxy ketone **9** underwent ketalization in high yields with methyl orthoformate under acidic conditions. Gassman-type conditions[15] applied to ketal **11** gave poor results. Interestingly, the conditions applied to ketal **7** (Ac_2O, pyridine, room temp.) were employed with ketal **11** to give enol ether **12**, which was obtained with a low conversion (20% after 18 h). At 65 °C, the conversion remained low with acetic anhydride (30%), but full conversion was



Scheme 2. Preparation of dienophiles **8** and **12**.

achieved after 18 h by using acetyl chloride. Although storable for months at 4 °C, the enol ether **12**, obtained in pure form in an overall 70% yield in three steps, proved to have a high sensitivity towards protic acidic media.[16]

[4+2] Heterocycloaddition

We selected for this study six heterodienes, all of which displayed a heterosubstituent able to deliver a hydroxy (**13a**,**b**) or amino (**13c**–**f**) group at the C-4' position of the target *C*-glycoside (Figure 2). These "prosugar" heterodienes were prepared according to literature procedures,[17–19] except for **13d**, which was obtained by treatment of **13b** with dibenzylamine.

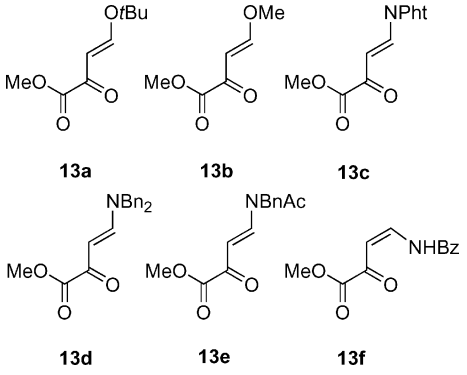


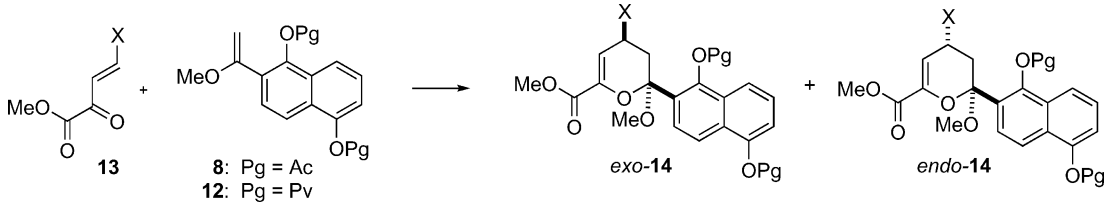
Figure 2. Heterodienes **13a**–**f**.

Previous results from model series have demonstrated that the heterocycloaddition reaction promoted by $SnCl_4$ between the heterodiene **13a** and α-methoxyvinylnaphthalene was completely "*exo*" selective.[20] This "*exo*" configuration appeared as the most favorable to give *C*-naphthyl glycosides in good yields and in a stereoselective manner by the HyBRedOx sequence. On the basis of these promising results, we applied the same conditions to dienophile **8** using 15 mol-% of $SnCl_4$ at 0 °C (Table 1, Entry 1). With heterodiene **13a**, "*exo*" selective heterocycloaddition proceeded in acceptable overall yields (46%), however, the main adduct was **14b** (X = OMe, **14b**/**14a** ratio = 2:1) due to the exchange in situ between the *tert*-butoxy group of the heterodiene and the methoxy group delivered by decomposition of enol ether **8**. Clearly, the use of methoxy-substituted **13b** solved this problem of exchange (Entries 2–4). Lowering the reaction temperature to –30 °C restricted the degradation of the substrates and significantly increased the yield of cycloadduct **14b**. Interestingly, depending on its final treatment, this reaction gave very different stereochemical results. Indeed, when the work-up was carried out at –30 °C with an aqueous saturated $NaHCO_3$ solution (Entry 4), poor diastereoselectivity (47/53) in favor of the adduct ***endo*-14b**, as a mixture of two separable diastereoisomers, was observed. In contrast, when the same aqueous treatment was performed at room temperature, the cycloaddition reaction led exclusively to the adduct ***exo*-14b** in 66% yield[21] as the consequence of a likely rapid epimerization at the ketal center[22] (Entry 3). This epimerization was exemplified by the following experiment: Treatment of the pure adduct ***endo*-14b** with 15 mol-% of $SnCl_4$ in DCM for 2 h from –30 to 0 °C led to its complete disappearance and the formation of the epimer ***exo*-14b**, together with the retro-Michael product **9′** (diacetate analogue of ketone **9**, Scheme 2). Semiempirical AM1 calculations using Spartan®[23] confirmed that ***exo*-14b** is approximately 2 kcal/mol more stable than ***endo*-14b** (Table 2).

The $SnCl_4$-catalyzed heterocycloaddition of the dipivaloyloxy dienophile **12**, conducted at –30 °C, displayed the same features as the acetate series (Entry 5). Again, the results depended strongly on the experimental conditions. When warming to room temperature prior to hydrolysis was too fast, and as a consequence the delay before hydrolysis too short, the reaction led to a 1:1 mixture of diastereoisomers ***endo*-14c** and ***exo*-14c**. In this case, total epimerization to the most stable isomer ***exo*-14c** (Table 2) could not be achieved although significant *exo* selectivity was obtained when aqueous treatment of the reaction mixture was carried out after a slow return to room temperature (2 h). Under these conditions, the cycloaddition reaction led mainly to adduct ***exo*-14c** with a 9:1 diastereoselectivity in 62% yield.

The two diastereoisomers were easily separable by chromatography on silica gel. Diastereoisomers were identified by comparison with the previously described cycloadduct **15** (Table 3).[12] Indeed, the chemical shifts and coupling constants of protons 3-H, 4-H, and 5-H are character-

Table 1. Heterocycloaddition reactions of dienophiles **8** and **12**.



Entry	Diene	X	Dienophile	Catalyst (mol-%)	Conditions	Adduct	% Yield	*exo*/*endo* selectivity[a]
1	**13a**	O*t*Bu	**8**	$SnCl_4$ (15)	CH_2Cl_2, 0 °C, 3 h	**14a**	15[b]	>97:3
2	**13b**	OMe	**8**	$SnCl_4$ (15)	CH_2Cl_2, 0 °C, 3 h	**14b**	15	>97:3
3	**13b**	OMe	**8**	$SnCl_4$ (15)	CH_2Cl_2, –30 °C, 2 h	**14b**	66	>97:3
4	**13b**	OMe	**8**	$SnCl_4$ (15)	CH_2Cl_2, –30 °C, 2 h[c]	**14b**	51	47:53
5	**13b**	OMe	**12**	$SnCl_4$ (15)	CH_2Cl_2, –30 °C, 3 h	**14c**	62	90:10
6	**13c**	NPht	**12**	$SnCl_4$ (15)	CH_2Cl_2, –30 °C, 2 h	**14d**	29	>97:3[d]
7	**13c**	NPht	**12**	$SnCl_4$ (50)	CH_2Cl_2, –50 °C, 1 h	**14d**	50	>97:3[d]
8	**13c**	NPht	**12**	[Cu^{II}(Ph-Box)] (10)	THF, –78 °C to room temp. 24 h	–	0[e]	
9	**13c**	NPht	**12**	[Eu(fod)$_3$] (10)	toluene, reflux 2d	–	0[e]	
10	**13f**	NHBz	**12**	[Eu(fod)$_3$] (10)	toluene, reflux 2d	–	0[e]	

[a] Diastereoselectivity determined by ^{1}H NMR analysis. [b] Mixed with 31% of adduct **14b**. [c] Work-up at –30 °C. [d] For *exo*-**14d**, a 5:1 mixture of two atropoisomers. [e] Complete degradation of the dienophile **12**.

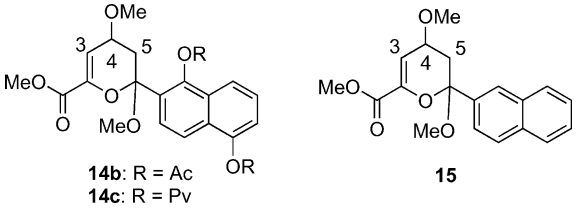
Table 2. Relative energies of the cycloadducts *endo*- and *exo*-**14a**–**d** (calculated with semiempirical method AM1).

Adduct	$E_{endo} - E_{exo}$ [kcal/mol]
14a	1.08
14b	2.11
14c	2.19
14d	3.18

istic of the *endo*/*exo* configuration of the cycloadducts. As examples, we can mention the typical large $^3J_{4H\text{-}5axH}$ coupling constant of the pseudoaxial position of 4-H in the *exo* form. This specific position of 4-H is also responsible for the low-field chemical shift of this proton in the *exo* form (ca. 4.4 ppm).

From the different aza-substituted heterodienes described in inverse-electron demand 1-oxa-Diels–Alder reactions with electron-rich dienophiles, the heterodiene **13c** bearing an *N*-phthalimido group at the C-4′ center is known to display the widest reactivity. Indeed, Tietze[24] and Jörgensen and their co-workers[25] obtained very good results with heterodiene **13c** in thermal or acid-catalyzed HDA reactions of vinyl ethers. Thus, we first initiated our study of the reactions of the aza series of this heterodiene with dienophile **12** under the conditions previously optimized for the methoxy heterodiene **13b**. Under these conditions (0.15 equiv. of $SnCl_4$, –30 °C for 2 h) the adduct **14d** could only be obtained in a modest yield (Table 1, Entry 6). A better result (Entry 7) was obtained by increasing the amount of $SnCl_4$ up to 50 mol-% while lowering the temperature to –50 °C. At this low temperature, the kinetics of the reaction could benefit from an increased quantity of promoter without increasing the degradation of the dienophile. Under these conditions adduct **14d** was readily obtained in 50% yield as a 5:1 mixture of two isomers, identical to those obtained at –30 °C. Note that in contrast to

Table 3. Comparison of the NMR signals **of 14b**, **14c**, and **15**.



	exo						*endo*					
	J [Hz]			*δ* [ppm]			*J* [Hz]			*δ* [ppm]		
	3-H–4-H	4-H–5_{eq}-H	4-H–5_{ax}-H	4-H	5_{eq}-H	5_{ax}-H	3-H–4-H	4-H–5_{eq}-H	4-H–5_{ax}-H	4-H	5_{eq}-H	5_{ax}-H
14b	1.8	[a]	[a]	4.38	3.11	1.82	[a]	[a]	[a]	3.80	3.02	2.23
14c	2.3	6.3	10.6	4.39	3.23	1.72	4.1	6.8	3.5	3.75	2.94	2.24
15	2	6.8	10.7	4.41	2.63	1.77	4.1	6.5	2.3	3.80	2.58	2.13

[a] Not determinable, due to coalescence at room temp.

adduct **14c**, variation of the experimental conditions (temperature and delay before hydrolysis) did not modify the diastereoisomeric ratio for adduct **14d**. Moreover, these diastereomers could not be separated by chromatography on silica gel. The three other aza-substituted heterodienes **13d**–**f** were treated under the new optimized conditions with $SnCl_4$, but, despite all our efforts, none of them afforded the desired heteroadduct. The conditions of Jörgensen and co-workers[25] using the [Ph-Box-Cu^{II}] complex as a chiral catalyst were also investigated with **13c** and **12**. Unfortunately, these conditions did not lead to the expected adduct: After aqueous treatment only ketone **9** resulting from the hydrolysis of the dienophile was isolated (Entry 8). Finally, the known *endo* selective catalyst [Eu(fod)$_3$] was tested with the aim of producing the adduct, from (*Z*)-heterodiene **13f**, that possesses the appropriate configuration for subsequent HyBRedOx transformation. However, the formation of cycloadducts starting from **13f** (or **13c**) was not observed, even after heating in toluene at reflux for an extended period of time (Entries 9 and 10).

Concerning the stereochemical outcome of the cycloaddition catalyzed by $SnCl_4$ between **13c** and **12**, we had to assume that both isomers of **14d** (in a 5:1 ratio) possess the same *exo* relative configuration. Indeed, if significant differences prevail between the chemical shifts of the pseudoequatorial proton (5_{eq}-H) of the CH_2 group (δ = 3.00 ppm for the major adduct and 2.21 ppm for the minor adduct), we observed a surprising similarity in the coupling constants that characterize the signals of all the protons of the dihydropyran ring. Moreover, comparison between these coupling constants and those of the adducts **14c** suggests that both isomers of **14d** possess the same relative configuration, the *N*-phthalimido group adopting the pseudoequatorial position that is characteristic of an *exo* adduct. In addition, we did not observe significant differences between the chemical shifts and coupling constants of the allylic (4-H) protons that differentiate *exo* and *endo* isomers.

Considering this body of proof, it seems that the diastereoisomerism observed in the NMR spectra relies on the presence of two stable atropoisomeric forms of the same *exo* adduct **14d** (Figure 3). The presence of two atropoisomers indicates that a sufficiently high rotational barrier exists between these two atropoisomers. The possible explanations for this high rotational barrier might be the restriction of free rotation around either the C(b)–C(c) bond (Figure 4) or the C(f)–O(g) bond of the pivaloyloxy group at C-1 of the naphthalene ring (Figure 5). To answer this question the energy profiles of the rotation around these bonds were cal-

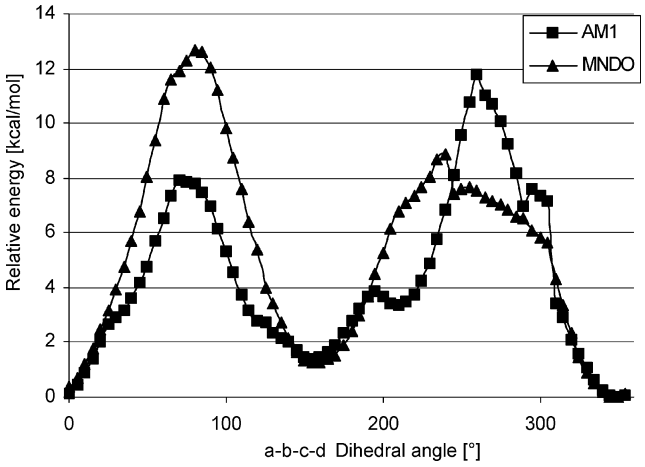


Figure 4. Energy profile for the rotation around the C(b)–C(c) bond of **14d**.

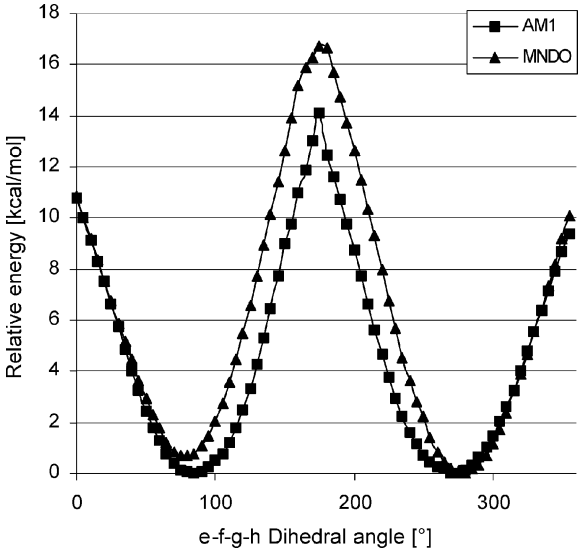


Figure 5. Energy profile for the rotation around the C(f)-O(g) bond of **14d**.

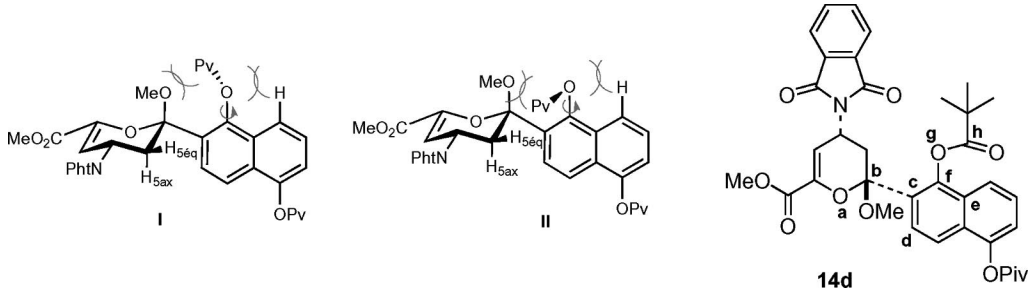


Figure 3. Atropoisomerism suggested for ***exo*-14d** adduct.

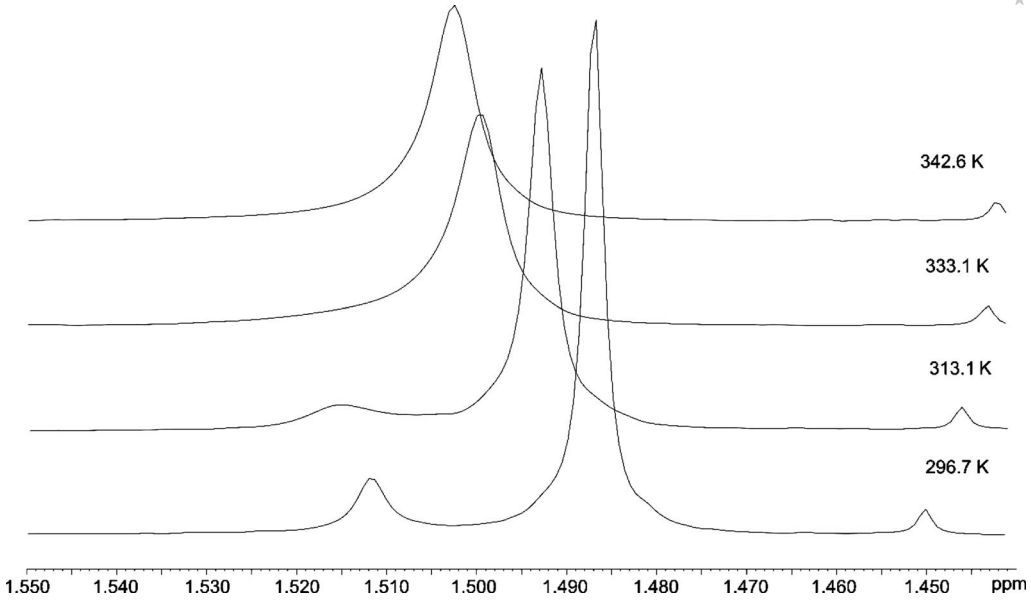
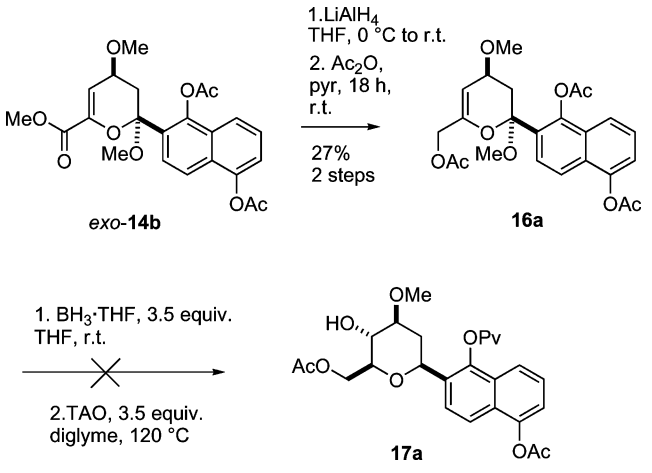


Figure 6. Temperature effect on the ^{1}H NMR spectra of ***exo*-14d**.

culated by using semiempirical methods (AM1, MNDO) for **14d**. The results of these studies are collected in Figures 4 and 5. Data were collected at intervals of 5°. The energy barriers calculated are close to 8 kcal/mol for the rotation around the C(b)–C(c) bond and close to 11 kcal/mol for the rotation around the C(f)–O(g) bond. The energy difference is high enough to assume that the restriction of the free rotation around the C–O bond of the pivaloyloxy group at C-1 of the naphthalene ring is responsible for the atropoisomerism observed. This perturbation of the free rotation is caused by the presence of the 8-H proton on one side and the bulky dihydropyrans on the other side. In fact, the pivaloyl group adopts an orientation orthogonal to the naphthalene ring with two energetically close states (Figure 5). The energy barrier for the rotation (evaluated as 11 kcal/mol) suggests an equilibrium between the two forms at room temperature that is sufficiently slow to allow observation of the two atropoisomers by NMR at room temperature. This assumption is in agreement with the fact that the stereochemical outcome of the cycloaddition was not affected by the conditions used. An NMR analysis of **14d** at high temperature confirmed this atropoisomeric phenomenon. Indeed, increasing the temperature from 25 to 70 °C produced the expected coalescence of the previously separated signals, namely the peaks corresponding to the three methyl groups of the pivaloyloxy group at the 1-position of the naphthalene ring (Figure 6).

Application of the HyBRedOx Sequence to Heteroadducts 14b,c

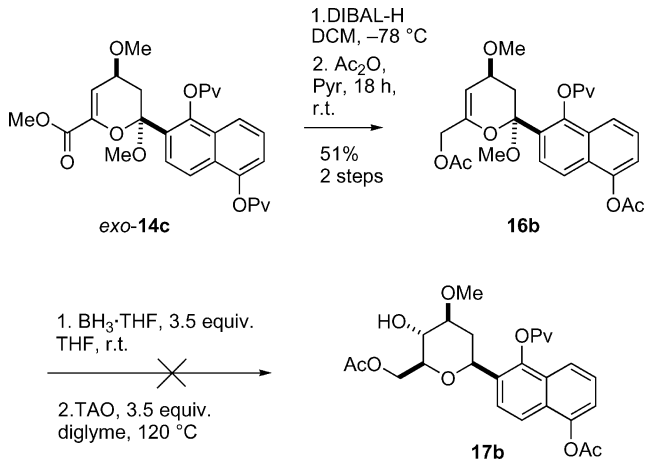
To access the *C*-glycosides the ester function of the ***exo*-14b** adduct was first reduced to the allylic alcohol by treatment with $LiAlH_4$ (Scheme 3). These conditions led to the deprotection of the acetates on the naphthalenediol. The crude reaction mixture was re-acetylated to afford triacetate **16a** in low yield. Triacetate **16a** was contaminated by non-identified byproducts. Next, we tested the tandem hydroboration/ketal reduction on compound **16a** by using BH_3·THF in THF at room temperature. Unfortunately, despite all our attempts, no product resulting from either hydroboration or ketal reduction was observed after treatment of **16a** with BH_3·THF and no tetrahydropyran structure was identified in the crude product after oxidative treatment.[26] Monitoring of the reaction by TLC showed that the starting material was still present before oxidation.



Scheme 3. Application of HyBRedOx to adduct **14b**.

Next we chose to focus on the pivaloyl-protected ***exo*-14c**. This type of protection is known to be more stable under basic and reducing conditions. Application of the HyBRedOx sequence required the prior chemoselective reduction of the conjugated ester group and not the pivalate groups located on the naphthalene ring. Hence we used diisobutylaluminium hydride (DIBAL-H) instead of $LiAlH_4$ to avoid deprotection of the pivaloyl function. Reduction

of the methyl ester function in ***exo*-14c** was efficiently carried out by using 3 equiv. of DIBAL-H at low temperature (Scheme 4). The resulting highly polar primary alcohol was acetylated without further purification to give compound **16b**, which displayed only one pivalate group and two acetate groups. Further experiments to prevent this unwanted selective reduction of the less hindered pivaloyl ester were unsuccessful or led to partial conversions.

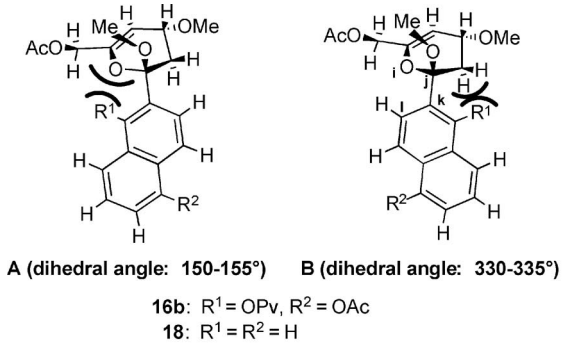


Scheme 4. Application of HyBRedOx to adduct **14c**.

The conditions tested on **16a** were applied to **16b** (BH_3·THF in THF at room temperature) for the tandem hydroboration/ketal reduction. Careful TLC monitoring of the reaction showed that hydroboration of **16** did not occur under standard conditions (BH_3·THF/BH_3Me_2S). Moreover, oxidative treatment with Me_3NO in refluxing diglyme[26] led to small quantities of dihydropyranic quinone as the sole isolated product, thus confirming the failure of the hydroboration/ketal reduction and the degradative side-oxidation of the naphthalene ring.

These disappointing results highlight two problems. The first is the lack of reactivity of the substrate towards borane, which is clearly related to the presence of functional groups on the naphthalene core. It was previously assumed that reduction of the ketal occurred after the hydroboration step.[12] According to this assumption, the HyBRedOx sequence could require a specific orientation of the axial methoxy group that would assist the approach of the borane to the double bond. The presence of a bulky substituent at the C-1 position of the naphthalene core could exclude this favorable conformation and thus explain the lack of reactivity.

Another explanation for the lack of reactivity can also be formulated if we consider that, in the HyBRedOx sequence, the ketal could be reduced before the hydroboration step. Although to the best of our knowledge, this type of reaction had never been reported in the literature, Brown and co-workers[27] reported an example of reduction of the ketal function of 2-methoxyflavan promoted by $NaBH_3CN$ in an acidic medium. This result suggests that due to the presence of an aromatic ring, even under mild conditions and in the absence of a strong Lewis acid, the ketal function could be reduced. On the basis of this result it is reasonable to argue that BH_3·THF without further assistance could promote the reduction of the ketal function of **18**[12] and that the presence of the naphthalene ring could play a crucial role in this reduction. Conjugation with the aromatic ring most probably acts to stabilize the transition state and favors the boron-assisted abstraction of the ketalic methoxy group by a positive overlap with the anti-bonding orbital of the C–O bond. This overlap would require a specific orientation of the naphthalene ring (Figure 7). However, in the case of **16b**, the presence of the pivaloyloxy group could disfavor this specific conformation (Figure 7, conformations A and B).



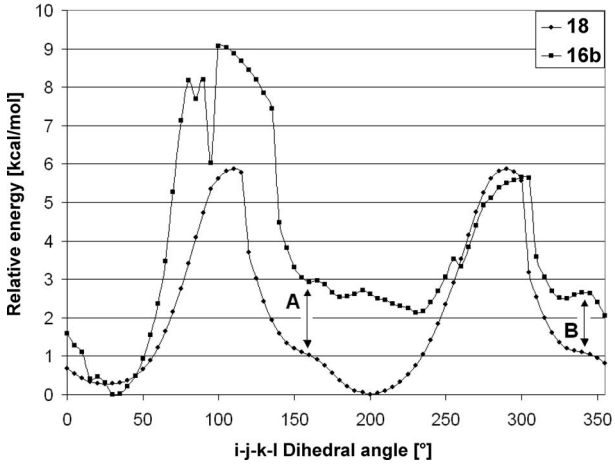


Figure 7. Energy profile for rotation around the C(j)–C(k) bond.

A comparison of the energy profiles shows that for compound **16b**, the two conformations corresponding to the previously cited criteria are higher by 1.5–2 kcal/mol than those of the corresponding free naphthyl **18**. The pivaloyl group would be responsible for a negative steric interaction with the CH_2 of the dihydropyran on one side and the oxygen of the dihydropyran ring on the other. These interactions are probably sufficient to prevent reduction of the ketal. Considering the second step, hydroboration is well known to be very sensitive to the bulkiness around the double bond. Thus, the steric decompression created by the reduction of the ketal function is probably necessary to achieve the hydroboration.

The last problem concerns the sensitivity of the 1,5-bis-(acyloxy)naphthalene core towards oxidative conditions, attested by the (low-yielding) formation of a dihydropyran byproduct bearing a naphthoquinone moiety together with a dihydropyran moiety unchanged with respect to **16b**. This propensity to oxidative degradation under the conditions used[26] (Me_3NO, diglyme, 120 °C) was confirmed by a complementary assay carried out on 1,5-diacetoxynaphthalene.

Conclusions

In this study we have accessed two new dienophiles of interest for the synthesis of complex *C*-aryl glycosides. These dienophiles were successfully involved in heterocycloaddition reactions with selected heterodienes bearing oxygen or nitrogen substituents at the C-4′ position. To the best of our knowledge this is the first report of a heterocycloaddition reaction involving a polyfunctionalized vinylnaphthalene as the dienophile.

This study has demonstrated that the HyBRedOx sequence is not compatible with the functionality introduced into the *C*-naphthyl substrate, which is necessary for subsequent oxidative transformation to the ultimate (bromo)-naphthoquinone. Indeed, the conformation adopted by the dihydropyran in the reduced adducts **16a**,**b** seems to prevent the borane reagent from undergoing to the tandem reaction. If this proposed interpretation could be confirmed, a more convenient case for the application of the "HyBRedOx" sequence could concern derivatives of the 5-hydroxynaphthyl series, which may be able to undergo "HyBRedOx", as in the model series, and might also be conveniently oxidized to bromonaphthoquinone.

Experimental Section

General: Air- and/or moisture-sensitive reactions were carried out with anhydrous solvents under argon in oven/flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2 from CaH_2. Commercial reagents were purchased from Aldrich, Acros, Fluka and, unless otherwise noted, were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Nuclear magnetic resonance (NMR) spectra were acquired with a Bruker Avance 400 spectrometer operating at 400 and 100 MHz for ^1H and ^{13}C, respectively; chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane, and coupling constants (J) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br. = broad. Infrared spectra were recorded with an FT-IR Nicolet Avatar 370 DTGS spectrometer (Thermo Electron Corp.) and reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded with a GCT Premier Micromass instrument.

1,5-Diacetoxy-2-(1-methoxyvinyl)naphthalene (8): Trimethyl orthoformate (4.56 mL, 10 equiv.) was added to a solution of 1-(1,5-dihydroxynaphthalen-2-yl)ethanone (**6**; 1 g, 4.1 mmol) in methanol (20 mL) at room temperature. One drop of concd. H_2SO_4 was added and the reaction mixture was stirred for 18 h at room temperature. The mixture was neutralized with Et_3N (1 mL) before concentration in vacuo to give a brown oil. Ac_2O (1.4 mL, 5 equiv.) was added to a solution of the crude product in pyridine (20 mL) at room temperature. The reaction mixture was stirred for 18 h at room temperature and then quenched with a cold and saturated $NaHCO_3$ solution. The reaction mixture was then extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (EtOAc/Cy, 3:7 + 1% of Et_3N) to afford 983 mg of a colorless oil (3.20 mmol, 78%, 2 steps). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, Ac), 2.46 (s, 3 H, Ac), 3.74 (s, 3 H, OMe), 4.45 (d, $^2J_{H,H}$ = 2.8 Hz, 1 H, 10-H), 4.53 (d, $^2J_{H,H}$ = 2.8 Hz, 1 H, 10-H), 7.28 (dd, $^4J_{H,H}$ = 1.0, J = 7.6 Hz, 1 H, 6-H), 7.50 (dd, $^3J_{H,H}$ = 7.6, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7-H), 7.60 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 3-H), 7.74–7.73 (m, 2 H, 4-H and 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.87, 20.94, 55.4, 86.7, 118.7, 118.9, 119.5, 126.3, 127.0, 127.8, 128.8 (2 C), 143.9, 146.7, 158.7, 169.0, 169.3 ppm. IR: $\tilde{\nu}$ = 1762, 1687 cm^{-1}. HRMS (CI+): calcd. for $C_{17}H_{17}O_5$ $[M + H]^+$ 301.1076; found 301.1085.

1-(1,5-Dipivaloxynaphthalen-2-yl)ethanone (9): Pivaloyl chloride (772 µL, 5 equiv.) was added dropwise to a solution of **6** (1.05 g, 5.2 mmol) in pyridine (50 mL) at room temperature. The reaction mixture was stirred at 65 °C for 18 h and then, after being cooled to room temperature, was quenched with a cold and saturated $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc. The organic layers were dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (EtOAc/Cy, 3:7) to afford 1.8 g of a white solid (4.62 mmol, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, Pv), 1.52 (s, 9 H, Pv), 2.60 (s, 3 H, Ac), 7.33 (dd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 7.5 Hz, 1 H, 6-H), 7.55 (dd, $^3J_{H,H}$ = 7.5, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7-H), 7.80 (br. s, 2 H, 3-H, 4-H), 7.87 (dd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 8.6 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (3 C), 27.3 (3 C), 29.6, 39.0 (2 C), 119.0, 120.3, 120.4, 125.4, 126.9, 127.6, 128.9, 129.7, 145.8, 146.8, 176.3, 176.6, 197.8 ppm. IR: $\tilde{\nu}$ = 2976, 1750, 1684, 1629, 1599, 1480, 1462 cm^{-1}. HRMS (CI+): (*m*/*z*): calcd. for $C_{22}H_{27}O_5$ $[M + H]^+$ 371.1858; found 371.1874.

6-Acetyl-2-bromo-5-pivaloxy-1,4-dihydronaphthalene-1,4-dione (10): NBS (100 mg, 6 equiv.) in a 1:2 mixture of acetic acid and water (3 mL) was added dropwise to a solution of **9** (37 mg, 0.1 mmol) in acetic acid (1 mL) at room temperature. The reaction mixture was stirred at 70 °C for 1 h and then, after being cooled to room temperature, quenched with cold water. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (EtOAc/Cy, 3:7) to afford 23 mg of an orange solid (0.061 mmol, 61%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, Pv), 2.58 (s, 3 H, Ac), 7.42 (s, 1 H, 3-H), 7.95 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 7-H), 8.17 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4 (3 C), 30.1, 39.0, 125.1, 126.1, 133.8, 133.9, 134.0, 141.9, 142.9, 144.4, 177.0, 177.1, 180.3, 197.4 ppm. HRMS (FI+): calcd. for $C_{17}H_{15}O_5{}^{79}Br$ $[M]^{+\cdot}$ 378.0103; found 378.0119.

2-(1-Methoxyvinyl)-1,5-dipivaloxynaphthalene (12): Trimethyl orthoformate (5.3 mL, 10 equiv.) was added to a solution of **9** (1.48 g, 4.00 mmol) in methanol (40 mL) at room temperature. One drop of concd. H_2SO_4 was added and the reaction mixture was stirred for 18 h at room temperature. The mixture was neutralized by addition of Et_3N (1 mL) and concentrated in vacuo to give 450 mg

of a red oil. The crude product was dissolved in pyridine (50 mL) and acetyl chloride (1.4 mL, 5 equiv.) was added at room temperature. The reaction mixture was stirred for 18 h at 65 °C and then quenched with a cold and saturated $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (EtOAc/Cy, 3:7 + 1% of Et_3N) to afford 1.33 g of a colorless oil (3.40 mmol, 85%, 2 steps). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, Pv), 1.48 (s, 9 H, Pv), 3.70 (s, 3 H, OMe), 4.42 (d, $^2J_{H,H}$ = 8.5 Hz, 1 H, 10-H), 4.43 (d, $^2J_{H,H}$ = 8.5 Hz, 1 H, 10-H), 7.23 (dd, $^4J_{H,H}$ = 1.1 Hz, $^3J_{H,H}$ = 7.5 Hz, 1 H, 6-H), 7.48 (dd, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 7-H), 7.55 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 3-H), 7.67 (dd, $^4J_{H,H}$ = 1.1 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 8-H), 7.73 (dd, $^4J_{H,H}$ = 1.1 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3 (3 C), 27.4 (3 C), 39.3, 39.5, 55.3, 86.7, 118.7, 118.8, 119.5, 126.3, 127.3, 127.7, 128.1, 128.8, 144.1, 146.9, 158.7, 176.3, 176.6 ppm. IR: $\tilde{\nu}$ = 2974, 1747, 1621, 1604, 1480, 1460 cm^{-1}. HRMS (CI+): calcd. $C_{23}H_{29}O_5$ $[M + H]^+$ 385.2015; found 385.2032.

Methyl (*E*)-4-(Dibenzylamino)-2-oxo-3-butenoate (13d): Dibenzylamine (187 µL, 1.5 equiv.) was added dropwise to a solution of heterodiene **13b** (100 mg, 0.63 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred for 2 h. After concentration in vacuo, the residue obtained was purified by chromatography on silica gel (EtOAc/Cy, 2:8) to afford 162 mg of a yellow solid (0.522 mmol, 83%). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, Me), 4.36 (s, 2 H, CH_2), 4.46 (s, 2 H, CH_2), 6.14 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H, 3-H), 7.13–7.20 (m, 4 H, H_{ar}), 7.31–7.40 (m, 6 H, H_{ar}), 8.20 (d, $^3J_{H,H}$ = 12.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.6, 52.3, 59.2, 92.1, 127.2, 127.7 (2 C), 127.9, 128.4, 128.8 (2 C), 128.9 (2 C), 133.9, 134.6, 158.7, 156.0, 164.6, 178.7. IR: $\tilde{\nu}$ = 3033, 1719, 1654, 1639, 1548, 1435 cm^{-1}. HRMS (FI+): calcd. for $C_{19}H_{19}NO_3$ $[M]^{+\cdot}$ 309.1365; found 309.1346.

Methyl (4*R,6*R**)-4-*tert*-Butoxy-6-(1′,5′-diacetoxynaphthalen-2′-yl)-5,6-dihydro-6-methoxy-4*H*-pyran-2-carboxylate (*exo*-14a):** Heterodiene **13a** (144 mg, 1 equiv.) in dichloromethane (1 mL) was added to a solution of dienophile **8** (216 mg, 0.72 mmol) in dry dichloromethane (5 mL). The reaction mixture was placed in a cooled bath at 0 °C. A 1 M solution of $SnCl_4$ in dichloromethane (0.11 mL, 0.15 equiv.) was added dropwise. After 3 h at 0 °C, the reaction mixture was hydrolyzed by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 50:50) to afford 111 mg of a 1:2 inseparable mixture of ***exo*-14a**/***exo*-14b** as a colorless oil (0.33 mmol, 46%).

***exo*-14a** (analytical sample): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 9 H, *t*Bu), 1.77–1.83 (m, 1 H, 5_{ax}-H), 2.43 (s, 3 H, OAc), 2.46 (s, 3 H, OAc), 2.93–3.04 (m, 4 H, 6-OMe + 5_{eq}-H), 3.85 (s, 3 H, CO_2Me), 4.61–4.66 (m, 1 H, 4-H), 6.17 (dd, $^3J_{H,H}$ = 1.8 Hz, $^4J_{H,H}$ = 2.0 Hz, 1 H, 3-H), 7.30 (dd, $^4J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6′-H), 7.51 (dd, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7′-H), 7.68 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 8′-H), 7.85–7.96 (m, 2 H, H_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 21.2, 28.1 (3 C), 30.2, 52.2, 61.6, 74.6, 102.4, 112.9, 117.0, 119.2, 119.5, 125.8, 126.4, 128.1, 128.6, 129.2, 139.9, 144.7, 146.5, 162.9, 169.3 (2 C) ppm. HRMS (FI+): calcd. for $C_{26}H_{30}O_9$ $[M]^{+\cdot}$ 486.1890; found 486.1884.

Methyl (4*R,6*R**)-6-(1′,5′-Diacetoxynaphthalen-2′-yl)-5,6-dihydro-4,6-dimethoxy-4*H*-pyran-2-carboxylate (*exo*-14b):** Heterodiene **13b** (374 mg, 1.2 equiv.) in dichloromethane (2 mL) was added to a solution of dienophile **8** (650 mg, 2.17 mmol) in dry dichloromethane (10 mL). The reaction mixture was placed in a cooled bath at –30 °C. A 1 M solution of $SnCl_4$ in dichloromethane (0.32 mL, 0.15 equiv.) was added dropwise. After 2 h at –30 °C, the temperature was slowly increased to room temperature and then the reaction mixture was hydrolyzed by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford 635 mg of ***exo*-14b** as a colorless oil (1.43 mmol, 66%). ^1H NMR (400 MHz, $CDCl_3$): δ =1.78–1.86 (m, 1 H, 5_{ax}-H), 2.44 (s, 6 H, 2 OAc), 2.99 (s, 3 H, 6-OMe), 3.08–3.14 (m, 1 H, 5_{eq}-H), 3.42 (s, 3 H, 4-OMe), 3.87 (s, 3 H, CO_2Me), 4.34–4.45 (m, 1 H, 4-H), 6.35 (dd, $^3J_{H,H}$ = 1.8 Hz, $^4J_{H,H}$ = 2.1 Hz, 1 H, 3-H), 7.39 (dd, $^4J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6′-H), 7.57 (dd, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7′-H), 7.81–7.86 (m, 3 H, H_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.1, 29.7, 52.4 (2 C), 56.1, 69.3, 102.5, 113.0, 117.0, 119.2, 119.4, 125.8, 126.4, 128.2, 128.6, 129.2, 141.2, 145.1, 147.0, 163.0, 169.2, 169.3 ppm. IR: $\tilde{\nu}$ = 2940, 1765, 1731, 1655, 1603, 1563, 1438, 1366, 1165 cm^{-1}. HRMS (FI+): calcd. for $C_{23}H_{24}O_9$ $[M]^{+\cdot}$ 444.1420; found 444.1403.

Methyl (4*R,6*R**)-6-(1′,5′-Diacetoxynaphthalen-2′-yl)-5,6-dihydro-4,6-dimethoxy-4*H*-pyran-2-carboxylate (*endo*-14b):** Heterodiene **13b** (120 mg, 1.2 equiv.) in dichloromethane (1 mL) was added to a solution of dienophile **8** (200 mg, 0.66 mmol) in dichloromethane (7.5 mL). The reaction mixture was placed in a cooled bath at –30 °C. A 1 M solution of $SnCl_4$ in dichloromethane (70 µL, 0.15 equiv.) was added dropwise. After 2 h at –30 °C, the reaction mixture was hydrolyzed by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford 80 mg of ***endo*-14b** (R_f = 0.35, 0.18 mmol, 27%) and 70 mg of ***exo*-14b** (R_f = 0.19, 0.16 mmol, 24%) as colorless oils. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.27 (m, 1 H, 5_{ax}-H), 2.44 (br. s, 3 H, OAc), 2.47 (s, 3 H, OAc), 2.95–3.07 (m, 4 H, 6-OMe + 5_{eq}-H), 3.46 (s, 3 H, 4-OMe), 3.77–3.84 (m, 1 H, 4_{ax}-H), 3.88 (s, 3 H, CO_2Me), 6.47 (br. s, 1 H, 3-H), 7.31 (dd, $^4J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 7.6 Hz, 1 H, 6′-H), 7.52 (dd, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7′-H), 7.71 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 8′-H), 7.79–7.83 (m, 2 H, H_{ar}) ppm.

Methyl (4*R,6*R**)-6-(1′,5′-Dipivaloxynaphthalen-2′-yl)-5,6-dihydro-4,6-dimethoxy-4*H*-pyran-2-carboxylate (14c):** Heterodiene **13b** (60 mg, 1.2 equiv.) in dichloromethane (1 mL) was added to a solution of dienophile **12** (300 mg, 0.78 mmol) in dichloromethane (2 mL). The reaction mixture was placed in a cooled bath at –30 °C. A 1 M solution of $SnCl_4$ in dichloromethane (0.11 mL, 0.15 equiv.) was added dropwise. After 2 h at –30 °C the temperature was slowly increased to room temperature and then the reaction mixture was hydrolyzed by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine, and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford 230 mg of ***exo*-14c** (R_f = 0.29, 0.45 mmol, 57%) and 20 mg of ***endo*-14c** (R_f = 0.18, 0.04 mmol, 5%).

***exo*-14c**, major isomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, Pv), 1.51 (s, 9 H, Pv), 1.72 (dd, $^3J_{H,H}$ = 10.6 Hz, $^2J_{H,H}$ =

13.1 Hz, 1 H, 5_{ax}-H), 2.96 (s, 3 H, 6-OMe), 3.23 (ddd, $^4J_{H,H}$ = 1.7 Hz, $^3J_{H,H}$ = 6.3 Hz, $^2J_{H,H}$ = 13.1 Hz, 1 H, 5_{eq}-H), 3.41 (s, 3 H, 4-OMe), 3.87 (s, 3 H, CO_2Me), 4.39 (ddd, $^3J_{H,H}$ = 2.3 Hz, $^3J_{H,H}$ = 6.3 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, 4_{ax}-H), 6.23 (dd, $^4J_{H,H}$ = 1.7 Hz, *J* = 2.3 Hz, 1 H, 3-H), 7.26 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, 6′-H), 7.47–7.53 (m, 2 H, 7′-H + 8′-H), 7.80–7.84 (m, 1 H, 3′-H), 8.03 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (3 C), 27.4 (3 C), 39.4, 39.4, 51.3, 52.3, 56.7, 69.3, 100.3, 111.9, 118.8, 119.0, 119.3, 119.6, 125.5, 126.3, 128.3, 128.7, 129.3, 141.0, 144.9, 146.9, 163.0, 176.1, 176.7 ppm. IR: $\tilde{\nu}$ = 2959, 1720, 1655, 1587, 1550, 1436 cm^{-1}. HRMS (FI+): calcd. for $C_{29}H_{36}O_9$ $[M]^+$ 528.2359; found 528.2359.

***endo*-14c**, major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, Pv), 1.51 (s, 9 H, Pv), 2.24 (dd, $^3J_{H,H}$ = 6.8, $^3J_{H,H}$ = 14.8 Hz, 1 H, 5_{ax}-H), 2.94 (ddd, $^3J_{H,H}$ = 1.8, $^3J_{H,H}$ = 3.5, $^3J_{H,H}$ = 14.8 Hz, 1 H, 5_{eq}-H), 3.03 (s, 3 H, 6-OMe), 3.42 (s, 3 H, 4-OMe), 3.75 (ddd, $^3J_{H,H}$ = 3.5, $^3J_{H,H}$ = 4.1, $^3J_{H,H}$ = 6.8 Hz, 1 H, 4_{eq}-H), 3.88 (s, 3 H, CO_2Me), 6.43 (dd, $^3J_{H,H}$ = 1.3, $^3J_{H,H}$ = 4.1 Hz, 1 H, 3-H), 7.26 (dd, $^3J_{H,H}$ = 1.6, $^3J_{H,H}$ = 7.3 Hz, 1 H), 7.45–7.60 (m, 2 H), 7.80–7.84 (m, 2 H) ppm.

Methyl (4*R,6*R**)-6-(1′,5′-Dipivaloxynaphthalen-2′-yl)-5,6-dihydro-6-methoxy-4-phthalimido-4*H*-pyran-2-carboxylate (14d):** Heterodiene **13c** (164 mg, 0.633 mmol) in dichloromethane (1 mL) was added to a solution of dienophile **12** (364 mg, 1.5 equiv.) in dichloromethane (2 mL). The reaction mixture was placed in a cooled bath at –30 °C. A 1 M solution of $SnCl_4$ in dichloromethane (0.311 mL, 0.5 equiv.) was added dropwise. After 2 h at –30 °C the temperature was slowly increased to room temperature and then the reaction mixture was hydrolyzed by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 90:10) to afford 212 mg of a 5:1 inseparable mixture of two diastereoisomers ***exo*-14d** (0.316 mmol, 50%).

Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, Pv), 1.52 (s, 9 H, Pv), 2.46 (dd, $^3J_{H,H}$ = 12.4, $^2J_{H,H}$ = 12.8 Hz, 1 H, 5_{ax}-H), 3.00 (ddd, $^4J_{H,H}$ = 1.7, $^3J_{H,H}$ = 6.3, $^2J_{H,H}$ = 12.8 Hz, 1 H, 5_{eq}-H), 3.05 (s, 3 H, 6-OMe), 3.85 (s, 3 H, CO_2Me), 5.51 (ddd, $^3J_{H,H}$ = 2.3, $^3J_{H,H}$ = 6.3, $^3J_{H,H}$ = 12.4 Hz, 1 H, 4_{ax}-H), 6.23 (dd, $^4J_{H,H}$ = 1.7, $^3J_{H,H}$ = 2.3 Hz, 1 H, 3-H), 7.26 (dd, $^4J_{H,H}$ = 1.3, $^3J_{H,H}$ = 7.3 Hz, 1 H, 6′-H), 7.47 (dd, $^3J_{H,H}$ = 7.3, $^3J_{H,H}$ = 8.3 Hz, 1 H, 7′-H), 7.54 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, 8′-H), 7.67–7.74 (m, 2 H, 2 Phth-H), 7.80–7.88 (m, 3 H, 2 Phth-H + 3′-H), 8.10 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3 (3 C), 27.5 (3 C), 33.4, 39.4, 39.6, 41.7, 51.3, 52.4, 101.3, 112.7, 118.7, 119.2, 119.3, 123.4 (2 C), 125.8, 126.6, 128.2, 128.6, 129.2, 131.8 (2 C), 134.1 (2 C), 141.2, 145.1, 147.0, 162.5, 167.5 (2 C), 176.1, 176.8 ppm. IR: $\tilde{\nu}$ = 2974, 1748, 1714, 1621, 1604, 1480, 1460 cm^{-1}. HRMS (CI+): calcd. for $C_{36}H_{38}NO_{10}$ $[M + H]^+$ 644.2496; found 644.2519.

Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, Pv), 1.52 (s, 9 H, Pv), 2.21 (ddd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 6.3, $^2J_{H,H}$ = 12.8 Hz, 1 H, 5_{eq}-H), 2.54 (dd, $^3J_{H,H}$ = 12.4, $^2J_{H,H}$ = 12.8 Hz, 1 H, 5_{ax}-H), 3.32 (s, 3 H, 6-OMe), 3.84 (s, 3 H, CO_2Me), 5.43 (ddd, $^3J_{H,H}$ = 2.3, $^3J_{H,H}$ = 6.3, $^3J_{H,H}$ = 12.4 Hz, 1 H, 4_{ax}-H), 6.21 (dd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 2.3 Hz, 1 H, 3-H), 7.26 (m, 1 H, 6′-H), 7.49 (m, 1 H, 7′-H), 7.59 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 8′-H), 7.74–7.76 (m, 2 H, 2 Phth-H), 7.84–7.88 (m, 3 H, 2 Phth-H + 3′-H), 7.91 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, 4′-H) ppm.

(4*S,6*S**)-2-(Acetoxymethyl)-6-(1′,5′-diacetoxynaphthalen-2′-yl)-5,6-dihydro-4,6-dimethoxy-4*H*-pyran (16a):** $LiAlH_4$ (1.01 mL, 1 M in THF, 3 equiv.) was added dropwise to a solution of adduct ***exo*-14b** (150 mg, 0.337 mmol) in dry THF (10 mL) at 0 °C. After 45 min, the temperature was increased to room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution at 0 °C. After removing THF in vacuo, the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was dissolved in pyridine (5 mL) and then acetic anhydride (320 μL, 10 equiv.) was added. After 18 h at room temperature, a saturated aqueous $NaHCO_3$ solution was added. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford 41 mg of **16a** (0.09 mmol, 27%) as a red oil.^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.79 (m, 1 H, 5_{ax}-H), 2.11 (s, 3 H, 1-OAc), 2.46 (s, 3 H, 1′-OAc), 2.47 (s, 3 H, 5′-OAc), 2.99 (s, 3 H, 6-OMe), 3.05–3.15 (m, 1 H, 5_{eq}-H), 3.37 (s, 3 H, 4-OMe), 4.25–4.33 (m, 1 H, 4-H), 4.59 (d, $^2J_{H,H}$ = 12.2 Hz, 1 H, 1A-H), 4.74 (m, 1 H, 1B-H), 5.26 (m, 1 H, 3-H), 7.30 (dd, $^4J_{H,H}$ = 1.0, *J* = 7.6 Hz, 1 H, 6′-H), 7.52 (dd, $^3J_{H,H}$ = 7.6, $^3J_{H,H}$ = 8.6 Hz, 1 H, 7′-H), 7.67 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, 3′-H), 7.79–7.85 (m, 2 H, 4′-H , 8′-H) ppm. HRMS (CI–): calcd. for $C_{24}H_{26}O_9$ $[M]^-$ 458.1577; found 458.1573.

(4*R,6*R**)-2-(Acetoxymethyl)-6-(5′-acetoxy-1′-pivaloxynaphthalen-2′-yl)-5,6-dihydro-4,6-dimethoxy-4*H*-pyran (16b):** DIBAL-H (1.13 mL, 1 M in toluene, 3 equiv.) was added dropwise to a solution of adduct ***exo*-14c** (200 mg, 0.378 mmol) in dry CH_2Cl_2 (4 mL) at –78 °C. After 45 min, the temperature was increased to 0 °C and excess of DIBAL-H was quenched by addition of methanol. A saturated aqueous NH_4Cl solution was added. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was dissolved in pyridine (5 mL) and then acetic anhydride (180 μL, 5 equiv.) was added. After 18 h at room temperature, a saturated aqueous $NaHCO_3$ solution was added. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine and then dried with anhydrous $MgSO_4$. The residue obtained after concentration in vacuo was purified by chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford 95 mg of **16b** (0.192 mmol, 51%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, Pv), 1.72 (dd, $^3J_{H,H}$ = 10.6, $^3J_{H,H}$ = 13.3 Hz, 1 H, 5_{ax}-H), 2.11 (s, 3 H, 1-OAc), 2.47 (s, 3 H, 1′-OAc), 2.96 (s, 3 H, 6-OMe), 3.21 (ddd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 6.3, $^2J_{H,H}$ = 13.3 Hz, 1 H, 5_{eq}-H), 3.37 (s, 3 H, 4-OMe), 4.29 (ddd, $^3J_{H,H}$ = 1.8, $^3J_{H,H}$ = 6.3, $^3J_{H,H}$ = 10.6 Hz, 1 H, 4-H), 4.59 (d, $^2J_{H,H}$ = 12.6 Hz, 1 H, 1A-H), 4.74 (d, $^2J_{H,H}$ = 12.6 Hz, 1 H, 1B-H), 5.25 (dd, $^4J_{H,H}$ = 1.5, $^3J_{H,H}$ = 1.8 Hz, 1 H, 3-H), 7.30 (dd, $^4J_{H,H}$ = 1.0, *J* = 7.6 Hz, 1 H, 6′-H), 7.50 (dd, $^3J_{H,H}$ = 7.6, $^3J_{H,H}$ = 8.7 Hz, 1 H, 7′-H), 7.57 (ddd, $^4J_{H,H}$ = 1.0, $^5J_{H,H}$ = 1.1, $^3J_{H,H}$ = 8.7 Hz, 1 H, 8′-H), 7.80 (dd, $^5J_{H,H}$ = 1.1, $^3J_{H,H}$ = 9.0 Hz, 1 H, 4′-H), 7.87 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 20.9, 27.4 (3 C), 36.1, 39.2, 50.8, 55.8, 63.4, 70.2, 101.6, 104.2, 118.9, 119.1, 119.5, 125.5, 126.3, 128.1, 129.0, 129.1, 145.0, 146.1, 146.6, 169.2, 170.5, 175.9 ppm. HRMS (CI–): calcd. for $C_{27}H_{32}O_9$ $[M]^-$ 500.2046; found 500.2068.

Supporting Information (see also the footnote on the first page of this article): ^{13}C NMR spectra and Spartan® calculations.

Acknowledgments

This work was supported by the "Région des Pays de la Loire" (CER 2000–2006, Ph. D. grant to L. M.).

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Received: July 2, 2008
Published Online: December 5, 2008

