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Tetrahedron Letters 48 (2007) 9056–9058
Tetrahedron Letters

Diels–Alder adducts from flavonoid

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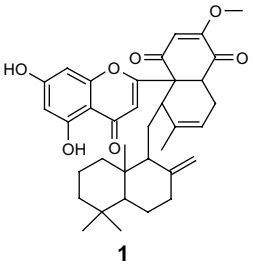
Received 19 July 2007; revised 21 August 2007; accepted 29 August 2007
Available online 18 October 2007

Abstract—A quinoflavonoid was synthesized from commercially available products over three steps. The quinoflavonoid turned out to be an excellent dienophile in Diels–Alder reaction. Reactions were easily performed in dichloromethane, and after evaporation of the solvent, expected products were obtained in good yields.

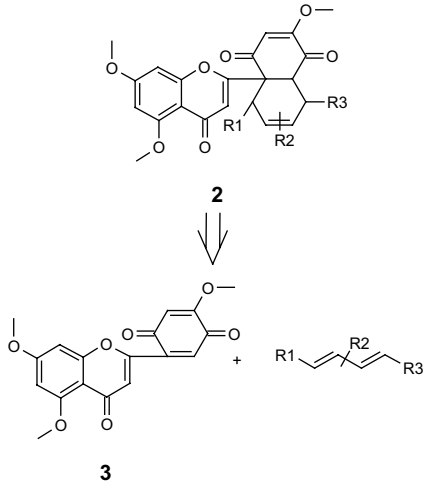
As a part of an ongoing screening program to find new proteinfarnesyltransferase (PFTAse) inhibitors, we have discovered a new series of meroterpene derivatives, of which compound **1** is an example (Fig. 1).

These compounds formally are Diels–Alder adducts of labdane-dienes with a quinone derived from a flavonoid. The originality of the structures and the hitherto rare observation of quinoflavonoids prompted us to investigate the total synthesis of such molecules. To know if such a compound as **1** might be obtained from a Diels–Alder reaction between a quinoflavonoid and a diene, we have decided to evaluate this approach by using a model reaction drawn in Scheme 1.



1

Figure 1. Meroterpene derivative.



Scheme 1. Retrosynthetic pathway.

The synthesis of the target quinoflavonoid **3** is outlined in Scheme 2. Esterification of the commercially available 2,4,5-trimethoxybenzoic acid **4** with dimethylsulfate in the presence of potassium carbonate in acetone gave the desired ester **5** in good yield (80%). Compound **5** was then reacted with ketone **6** in a Claisen-type condensation reaction using LiHMDS as a base.[1] After simple extractive work-up, the diketone was directly used in the next step without any further purification. The ring-closure reaction was performed under acidic conditions using 0.5% sulfuric acid in acetic acid to provide pentamethoxyflavone **7** in good yield (83% over two steps).

Keywords: Diels–Alder reaction; Quinoflavonoid.
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✠ Deceased on March, 20th 2006 during this research.

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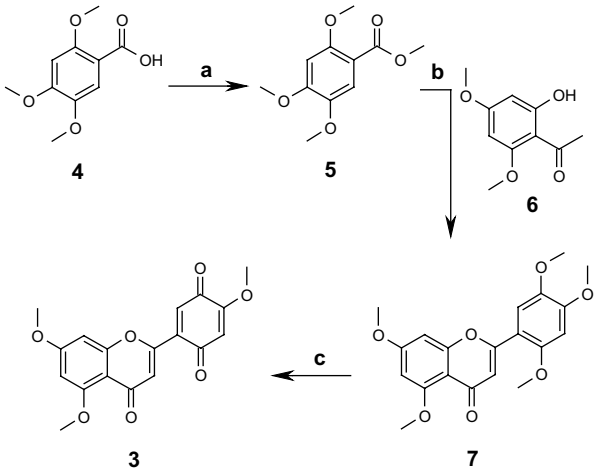
doi:10.1016/j.tetlet.2007.08.137



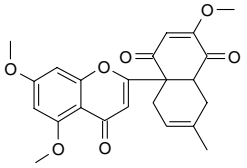
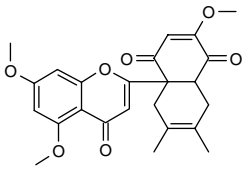
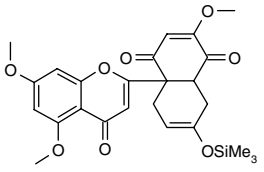
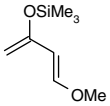
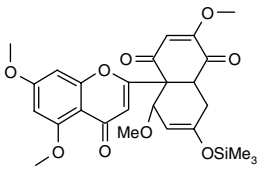
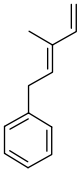
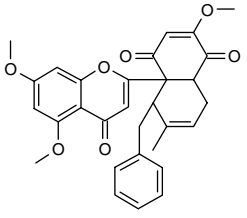
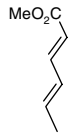
Scheme 2. Synthesis of the quinoflavonoid **3**. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, reflux, 80%; (b) (i) **6**, LiHMDS 1 M THF, anhydrous THF, argon; (ii) AcOH, H_2SO_4, reflux, 83% (for the two steps); (c) AgO, HNO_3 6 N, acetone, dioxane, rt, 24%.

Oxidative demethylation of **7** was carried out in a mixture of acetone–1,4-dioxane 1:1 in the presence of AgO and 6 N HNO_3 at room temperature.[2] The desired quinoflavonoid **3** was finally obtained after silica gel column chromatography in 24% yield.[3,6]

Quinoflavonoid **3** was then engaged in Diels–Alder reactions with different dienes (Table 1). All the reactions were performed in CH_2Cl_2. The progress of the reactions was monitored by HPLC (disappearance of quinoflavonoid **3**). After completion of the reactions, the volatiles were removed by evaporation under reduced pressure to yield practically pure Diels–Alder adducts.

The reaction with isoprene (entry 1) was initially performed at room temperature with only 1 equiv of diene. The reaction was not complete, even when further amounts of isoprene were added during the reaction. By using an ace pressure tube and heating at 50 °C, an essentially quantitative yield of the expected product was achieved. Thus, the reaction was repeated using the conditions described in entry 1. This approach led to compound **8** in an excellent yield.[6] The NMR spectrum indicated the presence of two regioisomers differing in the position of the methyl group on the carbon–carbon double bond. Structure of the major product is represented in Table 1. In entry 2, the Diels–Alder reaction was performed at room temperature with also an excess of 2,3-dimethylbutadiene and in a very good yield. Indeed, the reaction was initially started with 1 equiv of diene and 3.4 additional equivalents were added over 22 h to complete the reaction. Entries 3 and 4, with only 1 equiv of diene introduced, showed that the mesomeric (+M) effect of the methoxy group greatly increased the kinetics of the reaction. In both cases, the NMR spectra indicated the presence of only one regioisomer with good yields. However, with the commercially available Danishefsky's diene (entry 4),[5] the NMR spectrum was contaminated by a small amount of the ketone derivative that was initially

Table 1. Synthesis of Diels–Alder adducts from quinoflavonoid **3**

Entry	Diene	Conditions	Product (yield %)
1	 10.0 equiv	50 °C, 17 h[a]	 **8** (99) proportion of regioisomer 83:17
2	 4.4 equiv	rt, 22 h	 **9** (92)
3	 1.0 equiv	rt, 92 h	 **10** (93)
4	 1.0 equiv	rt, 15 min	 **11** (87)
5[b]	 1.0 equiv	rt, 41 h	 **12** (88)
6	 1.0 equiv	rt, eight days then 50 °C, 70 h[a]	No reaction

[a] The reaction was conducted in an ace pressure tube.
[b] For synthesis of the diene, see Ref. 4

present in the starting material (10%). Even with 1 equiv of a sterically hindered diene as used in entry 5, the Diels–Alder reaction worked well and gave only one regioisomer in a good yield. Finally, in entry 6 there was no reaction with 1 equiv of the desactivated diene methylsorbate. Even when the reaction was performed in an ace tube pressure for three days, the HPLC indicated that the two starting materials were still present.

In conclusion, we report a three step entry into a so far little-known family of products, the quinoflavonoids with 16% overall yield. Their Diels–Alder reaction with a variety of dienophiles was performed in a very simple procedure (CH_2Cl_2 as solvent, monitoring with HPLC, evaporation of volatiles) and under mild conditions (room temperature or 50 °C at maximum, neutral environment, no catalyst). Expected products were obtained in very good yields and with an excellent regioselectivity.

Acknowledgment

We wish to thank Pierre Fabre Medicament and the CNRS for their support of this research.

References and notes

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2. Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183–188.
3. Compound **3** has already been synthesized and described (mass, elemental analysis, and UV) in Hörhammer, L.; Wagner, H.; Rösler, H.; Keckeisen, M.; Farkas, L. *Tetrahedron* **1965**, *21*, 969–975.
4. Desai, S. R.; Gore, V. K.; Mayelvaganan, T.; Padmakumar, R.; Bhat, S. V. *Tetrahedron* **1992**, *48*, 481–490.
5. Danishefsky's diene was introduced in the following seminal paper: Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808; The further development of this diene motif is chartered in the following reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406; (b) Danishefsky, S. *Aldrichim. Acta* **1986**, 56–69.
6. *Physical and spectral data of compounds* (**3**, **8**–**12**): NMR spectra were all run in $CDCl_3$ at 500 MHz for ^1H and at 125 MHz for ^{13}C. Compound **3**: ^1H NMR: δ 7.38 (s, 1H), 7.30 (s, 1H), 6.47 and 6.38 (d, 1H, $J = 2.3$ Hz), 6.05 (s, 1H), 3.96, 3.91 and 3.89 (s, 3H); ^{13}C NMR: δ 183.9, 181.5, 176.6, 164.6, 161.0, 159.6, 158.3, 152.0, 136.1, 131.9, 119.1, 109.3, 109.1, 96.4, 92.5, 56.3, 55.8; ESITOFMS (positive mode) m/z 365.0625 $[M+Na]^+$ (calcd for $C_{18}H_{14}NaO_7$ 365.0632). Compound **8**: ^1H NMR: δ 6.36 and 6.35 (d, 1H, $J = 2.2$ Hz), 6.16 (s, 1H), 5.93 (s, 1H), 5.40 (m, 1H), 3.93 and 3.82 (s, 3H, ArOMe), 3.86 (s, 3H, OMe of the quinone part), 3.73 (dd, 1H, H at ring junction, $J = 5.6$ Hz), 2.74 and 2.45 (d, 1H, $J = 18$ Hz), 2.54 and 1.99 (dd, 1H, $J = 18$; 3.9 Hz), 1.67 (s, 3H); ^{13}C NMR: δ 195.4, 192.4, 176.9, 164.1, 163.1, 161.1, 160.9, 159.9, 132.0, 116.8, 112.8, 109.3, 108.9, 96.4, 92.4, 56.6, 56.4, 55.8, 55.7, 48.1, 30.0, 27.7, 23.1; ESITOFMS (positive mode) m/z 843. 3056 $[2M+Na]^+$, 433.1262 $[M+Na]^+$ (calcd for $C_{23}H_{22}NaO_7$ 433.1258); IR (diamond point): 2943, 1716, 1647, 1600, 1457, 1337, 1221, 1202, 1159, 1098, 823. Compound **9**: ^1H NMR: δ 6.36 and 6.34 (d, 1H, ArH, $J = 2.25$ Hz), 6.04 (s, 1H), 5.93 (s, 1H), 3.93 and 3.81 (s, 3H, ArOMe), 3.86 (s, 3H, OMe of the quinone part), 3.66 (dd, 1H, H at ring junction, $J = 5.9$ Hz), 2.71 and 2.32 (d, 1H, $J = 18.05$ Hz), 2.52 and 2.03 (dd, 1H, $J = 18$; 4.3 Hz), 1.67 and 1.62 (s, 3H); ^{13}C NMR: δ 195.2, 192.6, 176.9, 164.1, 163.4, 161.0, 160.9, 159.8, 123.6, 121.9, 112.4, 109.3, 108.9, 96.4, 92.4, 56.5, 56.4, 55.8, 55.7, 48.2, 35.7, 29.5, 18.7; ESITOFMS (positive mode) m/z 871.2944 $[2M+Na]^+$, 447.1399 $[M+Na]^+$ (calcd for $C_{24}H_{24}NaO_7$ 447.1414); IR (diamond point): 3087, 2844, 1713, 1655, 1601, 1457, 1421, 1334,1221, 1202, 1099, 845. Compound **10**: ^1H NMR: δ 6.36 and 6.35 (d, 1H, $J = 2.2$ Hz), 6.21 (s, 1H), 5.94 (s, 1H), 4.82 (m, 1H), 3.93, 3.86 and 3.84 (s, 3H), 3.81 (m, 1H), 2.76–2.64 (dt, 2H, $J = 17.8$; 2 Hz), 2.54 (dd, 1H, $J = 17.6$; 3.2 Hz), 2.04 (dd, 1H, $J = 18.5$; 4.1 Hz), 0.18 (s, 9H); ^{13}C NMR: δ 195.4, 191.6, 176.8, 164.4, 164.1, 162.4, 161.2, 159.9, 129.0, 113.2, 109.9, 109.3, 99.3, 96.4, 92.5, 56.6, 56.5, 55.8, 55.7, 48.5, 28.9, 26.8, 0.3; ESITOFMS (positive mode) m/z 507.1424 $[M+Na]^+$ (calcd for $C_{25}H_{28}NaO_8Si$ 507.1446); IR (diamond point): 2953, 1718, 1647, 1605, 1458, 1338, 1204, 1160, 1101, 843. Compound **11**: ^1H NMR: δ 6.36 and 6.35 (d,1H, $J = 2.0$ Hz), 6.17 (s, 1H), 6.04 (s, 1H), 5.21 (d, 1H, $J = 5.5$ Hz), 4.25 (d, 1H, $J = 5.6$ Hz), 3.93 (s, 3H), 3.86 (s, 6H), 3.74 (m, 1H), 3.14 (s, 3H), 3.03 (d, 1H, $J = 18.3$ Hz), 1.94 (dd, 1H, $J = 18.7$; 7.3 Hz), 0.21 (s, 9H); ^{13}C NMR: δ 195.1, 190.1, 176.5, 164.6, 164.1, 161.3, 160.9, 159.8, 153.6, 114.2, 111.8, 108.9, 100.4, 96.3, 92.5, 75.2, 59.7, 56.5, 55.8, 55.6, 46.2, 25.0, 0.2; ESITOFMS (positive mode) m/z 537.1551 $[M+Na]^+$ (calcd for $C_{26}H_{30}NaO_9Si$ 537.1551); IR (diamond point): 2963, 1719, 1653, 1604, 1458, 1334, 1204, 1159, 1106, 844. Compound **12**: ^1H NMR: δ 7.31–7.16 (m, 3H), 7.07 (d, 2H, $J = 7.2$ Hz), 6.36 and 6.34 (d, 1H, $J = 2.1$ Hz), 6.16 (s, 1H), 6.01 (s, 1H), 5.29 (m, 1H), 3.92, 3.87 and 3.86 (s, 3H), 3.78 (m, 1H), 3.19–3.11 (m, 2H), 2.80 (dd, 1H, $J = 13.5$; 4.6 Hz), 2.45 (dd, 1H, $J = 13.5$; 9.5 Hz), 2.08 (m, 1H), 1.31 (s, 3H); ^{13}C NMR: δ 196.1, 192.7, 176.9, 164.1, 163.7, 163.0, 160.9, 159.8, 139.8, 135.3, 128.8, 128.4, 126.6, 119.8, 113.4, 112.6, 111.3, 96.3, 92.5, 60.7, 56.6, 56.4, 55.7, 46.5, 45.9, 38.6, 24.0, 20.7; ESITOFMS (positive mode) m/z 523.1724 $[M+Na]^+$ (calcd for $C_{30}H_{28}NaO_7$ 523.1727); IR (diamond point): 2943, 1713, 1648, 1601, 1455, 1331, 1219, 1157, 1101, 824, 700.