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A novel and efficient route to the construction of the 4-oxa-tricyclo[4.3.1.0]decan-2-one scaffold

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Abstract—A short and efficient route to the synthesis of 4-oxa-tricyclo[4.3.1.0]decan-2-one scaffold **12** in good yield is reported. Essential to the synthesis was the implementation of selective protection of the catechol system in xanthone **2** with Ph_2CCl_2 and MOM groups. Subsequently, a biomimetic tandem Claisen/Diels–Alder reaction occurred to produce the desired tricyclic scaffold **11a** as a single isomer. A rationalization of the excellent region and stereoselectivity of this transformation was also proposed.

The intriguing 4-oxa-tricyclo[4.3.1.$0^{3,7}$]decan-2-one scaffold **12** is found in a growing class of biologically active natural products isolated from plants of the genus *Garcinia*. These compounds, including forbesione,[1] gambogic acid,[2] morellin,[3] lateriflorone,[4] and gaudichaudiones,[5] exhibit interesting antibacterial activity and cytotoxicity. Possibly, the 4-oxa-tricyclo[4.3.1.$0^{3,7}$]-decan-2-one moiety is responsible for the bioactivity since the planar xanthones alone do not show a marked biological profile.[6] This caged scaffold was first proposed and experimentally tested by Quillinan and Scheinwam in 1971 by means of a tandem Claisen/Diels–Alder rearrangement[7] and was further developed by Nicolaou and Li during their synthesis of 1-*O*-methylforbesione[8] in 2001.

Recently, Nicolaou and co-workers obtained two isomers of this caged scaffold in 16 steps by protecting the 1,3-dihydroxy of xanthone **9** with the MOM group during their total synthesis of gambogin.[9] In the present Letter, a new and convenient method is reported by using Ph_2CCl_2 first to protect the 5,6-dihydroxy functionality in xanthone **2** and then using the MOM group to selectively protect the 3-hydroxy in xanthone **3**, leaving the 1-hydroxy unaffected. Thus, only in 9 steps, the caged scaffold is obtained with just one isomer **11a**.

The cascade precursor **9** was synthesized as summarized in Scheme 1. Xanthone **2** was obtained in 52% yield through a $ZnCl_2$-mediated condensation of phloroglucinol **1** with 2,3,4-trihydroxybenzoic acid in $POCl_3$.[10] Then, compound **2** was treated with a variety of protecting agents under several conditions to selectively protect the 5,6-dihydroxy, but with the 1,3-dihydroxy unaffected. Firstly, attempt to form the acetonide of the catechol system of **2** through reaction with acetone/TsOH was completely ineffective. The use of triphosgene as a protecting group yielded a product that was highly unstable at room temperature. Fortunately, Ph_2CCl_2 effectively protected the 5,6-dihydroxy of xanthone **2**, giving the desired intermediate **3**. However, following the literature procedure,[11] the yield was very low when xanthone **2** reacted with Ph_2CCl_2 without any solvent. After several experimental attempts, we found that the best conditions, which involved treatment of **2** with Ph_2CCl_2 in diphenyl ether at 175 °C, could produce **3** in 85% yield. Then, various protecting groups and conditions, such as TBDMSCl, Ac_2O and MOMCl, were used to protect the 3-hydroxy group in **3**. MOMCl[12] was found to give optimum results when used in conjunction with NaH in DMF to afford **4** in 90% yield. Subsequent hydrogenolysis[13] of the two benzyl groups in this new product, followed by a reaction with 2-chloro-2-methylbutyne in the presence of K_2CO_3, KI

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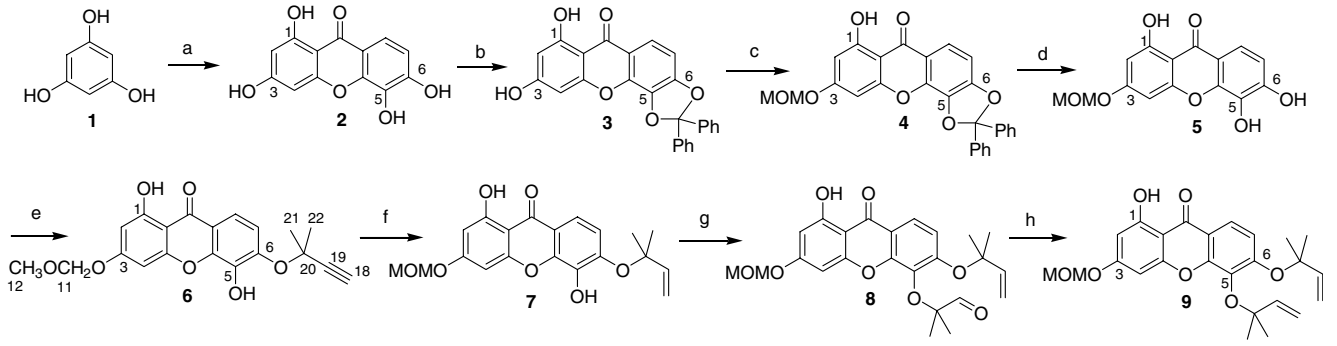
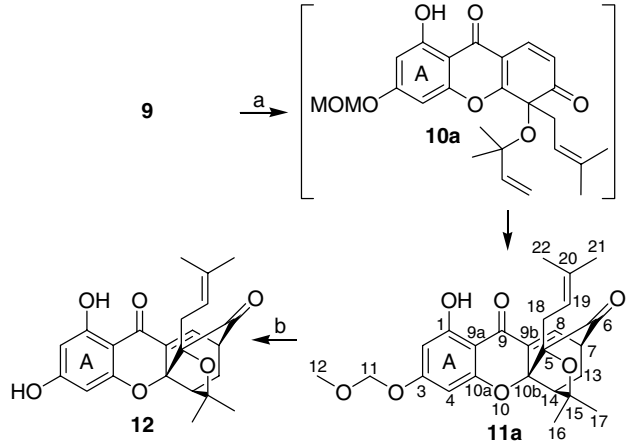


Scheme 1. Reagents and conditions: (a) 2,3,4-trihydroxybenzoic acid, $ZnCl_2$, $POCl_3$, 70 °C, 3 h, 52%; (b) Ph_2CCl_2, Ph_2O, 175 °C, 30 min, 85%; (c) MOMCl, NaH, DMF, 25 °C, 8 h, 90%; (d) Pd/C (10 wt %), H_2 (1 atm), THF/Et_2OH, 6 h, 95%; (e) 2-chloro-2-methylbutyne, KI, K_2CO_3, CuI, acetone, reflux, microwave irradiation, 20 min, 80%; (f) 10% Pd/$BaSO_4$, quinoline, EtOAc, 25 °C, 30 min, 95%; (g) *t*-BuOK, THF, 0 °C; then concentrated and suspended in MeCN; then 18[crown]-6, 15 min, bromoisobutyraldehyde, 0–25 °C, 1 h, 85%; (h) $CH_3P^+Ph_3Br^-$, NaHMDS, THF, 0–25 °C, 2 h, 85%.

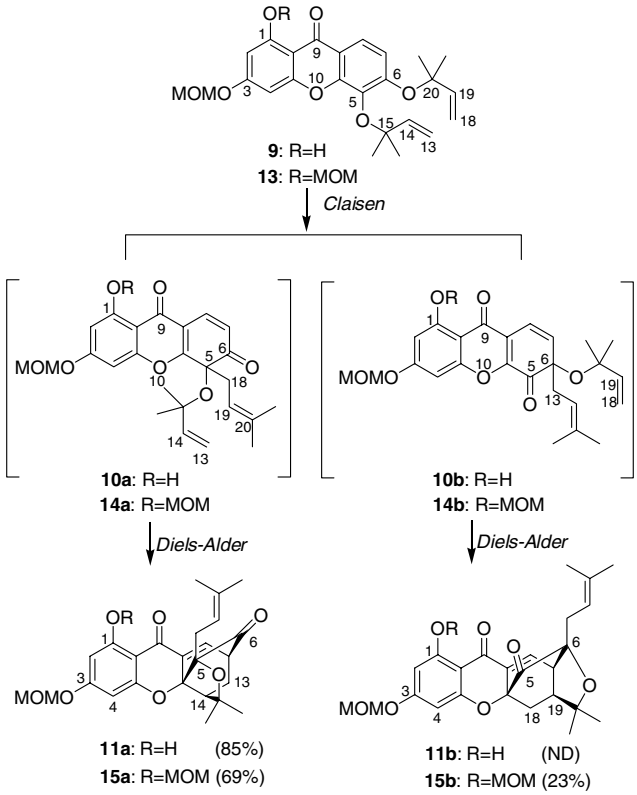
and catalytic CuI in refluxing acetone under microwave irradiation resulted in the formation of propargylic ether **6** in 76% overall yield. The propargylic ether group at C-6 instead of C-5 in compound **6** could be supported by NOE studies,[14] and the regioselectivity observed during this etherification of xanthone **5** could be explained as the C6–OH is *para* to the electronically deficient C9 carbonyl group of **5**, so that the C6–OH is much more active than C5–OH. Selective reduction (H_2, Lindlar catalyst) of the acetylenic group in compound **6** gave the corresponding olefin **7** in 95% yield. The potassium salt of **7**, generated by addition of *t*-BuOK, was suspended in CH_3CN and treated with α-bromoisobutyraldehyde in the presence of [18]crown-6 to afford **8** in 85% yield. Then, dialkene **9**was obtained in 85% yield by reaction of **8** with methylene phosphorane ($MeP^+Ph_3Br^-$, NaHMDS).[8]

Upon heating in DMF at 120 °C, the bis-(α,α-dimethylallyl) aryl ether **9** smoothly underwent the expected Claisen/Diels–Alder cascade sequence through the presumed intermediate **10a** to furnish **11a** in 85% yield (Scheme 2). The desired connectivity across the central tetrahydrofuran core of this compound was supported by HMBC studies.[15] Removal of the MOM group from the desired compound **11a** was smoothly effected through the action of HCl (1.0 M in CH_2Cl_2/Et_2O (1:1)), which generated the caged scaffold **12** in 90% yield.

The excellent regioselectivity observed during this tandem Claisen/Diels–Alder reaction deserves some comments. In principle, as in the case of diolefin **13** (Scheme 3), upon heating in DMF at 120 °C, the xanthone derivative **13** should smoothly undergo two different expected *ortho*-Claisen rearrangements, to afford



Scheme 2. Reagents and conditions: (a) DMF, 120 °C, 45 min, 85%; (b) HCl (1.0 M) in Et_2O/CH_2Cl_2 (1:1), 25 °C, 6 h, 90%.



Scheme 3. Possible isomers anticipated from the tandem Claisen/Diels–Alder reaction of compounds **4** and **13**.

structures **14a** and **14b**, which after the subsequent Diels–Alder reaction can produces adducts **15a** and **15b** in 69% and 23% yields, respectively.[9] However, in xanthone **9**, the absence of intermediate **10b** and the complete conversion of **9** to the desired regioisomer **10a** were observed. This preferential reaction path may be attributed to the C9 carbonyl group, the xanthone oxygen (O10), and the nature of the C1 functionality[16] in **9**.

The electronically deficient C9 carbonyl group of **9** is *para* to the C6 allyloxy unit. Thus, C9 can accept electron density from the C6 oxygen, which contributes to a weakening of the ether bond and facilitates rupture of the bond, yielding the C20 alkyl fragment, leading to intermediate **10a** (Scheme 3). In addition, as shown in the structure of **10a**, the xanthone oxygen (O10) is *meta* to the C6 carbonyl group, thereby stabilizing it by resonance. Such a stabilization effect cannot be achieved at the C5 carbonyl group of intermediate **10b**. Furthermore, in the case of **9** (R=H), the C9 carbonyl group is bound to the C1 OH by a hydrogen bond,[16] which increases its electronic deficiency. This leads to high selectivity of the Claisen rearrangement that produces intermediate **10a** exclusively and, following Diels–Alder reaction with the pendant C13-C14 dienophile, affords only**11a**as the regular caged scaffold. However, a partial loss of the site selectivity is observed with the 1,3-dimethoxymethoxy xanthone **13**. Apparently, the presence of the C1 methylene ether in **13** attenuates the electron withdrawing effect of the C9 carbonyl group, which reduces the preference for cleavage of the O–C20 bond and allows a competing rearrangement using the C5 allyloxy ether to take place. So, in the case of **13**, competition of these processes produces a mixture of Claisen adducts **14a** and **14b** and thereby a mixture of final products **15a** (regular caged scaffold) and **15b** (neo caged scaffold) in an approximate ratio of 3:1.

With this in mind, it appears that preinstalling all functionalities at the correct oxidation state in compound **9** triggers the desired rearrangement, producing the caged scaffold **11a** exclusively. Such regiochemical preference during this tandem rearrangement is also manifested in the vast majority of the *Garcinia* natural products, the structure of which is highlighted by the same homochiral scaffold.

In conclusion, we have presented an efficient and convenient synthesis of the caged scaffold **12**, an important intermediate for the total synthesis of many xanthone and xanthonoid natural products isolated from the *Garcinia* species of tropical plants. Our strategy highlights the use of selective protecting groups to form the important intermediate **5**, and the implementation of a biomimetic and completely regioselective Claisen/Diels–Alder cascade reaction to form the caged scaffold **11a** as a single isomer. The good yields of all intermediates and final products and relatively easy experimental procedures make this strategy a new and practical pathway to a biomimetic synthesis of related natural products.

Acknowledgments

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14. Spectral data for xanthone **6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.85 (s, 1H, C_1–OH), 7.76 (d, $J = 8.9$ Hz, 1H, C_8–H), 7.53 (d, $J = 8.9$ Hz, 1H, C_7–H), 6.71 (d, $J = 2.3$ Hz, 1H, C_2–H), 6.46 (d, $J = 2.3$ Hz, 1H, C_4–H), 5.80 (s, 1H, C_5–OH), 5.25 (s, 2H, C_{11}–H), 3.50 (s, 3H, C_{12}–H), 2.70 (s, 1H, C_{18}–H), 1.79 (s, 6H, C_{21}–H, C_{22}–H); The position of the MOM group at C_3–O was determined by the ROESY correlations between the signals at δ 5.25 (H-11) with 6.46 (H-4)/6.71 (H-2), a cross-peak observed in the ROESY spectrum between δ 1.79 (H-21, H-22) with 7.53 (H-7)/7.76 (H-8) confirmed that the position of the propargylic ether group was at C-6.
15. Spectral data for caged xanthone **11a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1H, C_1–OH), 7.44 (d, $J = 6.9$ Hz, 1H, C_8–H), 6.21 (d, $J = 2.0$ Hz, 1H, C_2–H), 6.18 (d, $J = 2.0$ Hz, 1H, C_4–H), 5.20 (s, 2H, C_{11}–H), 4.42–4.46 (m, 1H, C_{19}–H), 3.50–3.52 (m, 2H, C_{13}–H), 3.48 (s, 3H, C_{12}–H), 2.60–2.63 (m, 2H, C_{18}–H), 2.44 (d, $J = 9.6$ Hz, 1H, C_{14}–H), 2.34 (dd, $J_1 = 13.5$, $J_2 = 4.5$ Hz, 1H, C_7–H), 1.69 (s, 3H, C_{17}–H), 1.39 (s, 3H, C_{21}–H), 1.29 (s, 3H, C_{16}–H), 1.10 (s, 3H,

C_{22}–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 (C-6), 179.5 (C-9), 165.9 (C-3), 164.7 (C-9a), 160.9 (C-10a), 135.2 (C-8), 134.1 (C-20), 133.8 (C-9b), 118.3 (C-19), 101.7 (C-1), 97.0 (C-2), 95.5 (C-4), 94.0 (C-11), 90.3 (C-10b), 84.4 (C-5), 83.5 (C-15), 56.4 (C-12), 48.8 (C-14), 46.9 (C-13), 30.3 (C-17), 29.1 (C-18), 29.0 (C-16), 25.5 (C-21), 25.1 (C-7), 16.8 (C-22); The presence of phenol hydroxy group at δ 12.39 ppm, 2 aromatic proton signals at δ 6.21 (d, $J = 2.0$ Hz, 1H, C_2–H), δ 6.18 (d, $J = 2.0$ Hz, 1H, C_4–H), one methylene signal at δ 5.20 (s, 2H, C_{11}–H), one methyl signal at δ 3.48 (s, 3H, C_{12}–H) in the ^1H NMR spectrum (in chloroform-d_1) suggested that the A ring remained unchanged. One prenyl group was determined by the geminal methyl protons signals at δ 1.10 (s, 3H, C_{22}–H), δ 1.39 (s, 3H, C_{21}–H), the alkene proton signal at δ 4.42–4.46 (m, 1H, C_{19}–H) and the methylene signal at δ 2.60–2.63 (m, 2H, C_{18}–H). The structure of this prenyl group was further supported by the HMBC correlations between the signals at δ 2.60–2.63 (H-18) with 118.3 (C-19), δ 1.39 (H-21) with 16.8 (C-22)/118.3 (C-19)/134.1 (C-20) as well as the correlated signals at δ 1.10 (H-22) with 25.5 (C-21)/118.3 (C-19)/134.1 (C-20). The position of the prenyl group at C-5 was determined by the HMBC correlations between the signals at δ 2.60–2.63 (H-18) with 84.4 (C-5)/90.3 (C-10b)/202.9 (C-6). A cross-peak observed in the HMBC spectrum between δ 7.44 (H-8)/3.50–3.52 (H-13)/2.60–2.63 (H-18) with 202.9 (C-6) confirmed the position of the carbonyl group at carbon C-6. The connectivity between C-5 and C-10b was determined by long-range correlation between the signals at δ 90.3 (C-10b) with 7.44 (H-8)/2.60–2.63 (H-18) and 2.44 (H-14). Two methyl groups at C-15 were determined by the signals δ1.29 (H-16) with 30.3 (C-17)/48.4 (C-14)/83.5 (C-15) as well as the signals at δ 1.69 (H-17) with 29.0 (C-16)/48.8 (C-14)/83.5 (C-15).

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