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Total synthesis of (±)-nitidanin and novel procedures for determination of the location of the side chains on 1,4-benzodioxane

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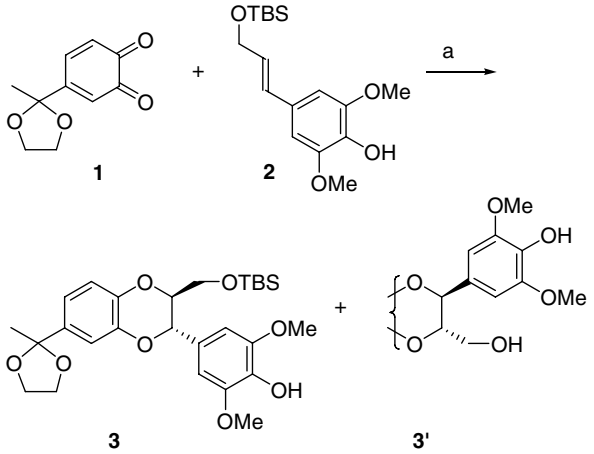
Abstract—Regioselective cycloaddition of *o*-quinone **4** and protected sinapyl alcohol **2** gave 1,4-benzodioxane **5**, which was converted to (±)-nitidanin (**6**), an antimalarial compound. Two novel procedures were developed to determine the location of the side chains of the adduct (**5**) based on partial ring cleavage.

We recently reported that a cycloaddition reaction of a stable *o*-quinone **1** and sinapyl alcohol unit **2** gave 1,4-benzodioxanes **3** and **3′** (**3**/**3′** = 2:1).[1] Although the regiochemistry of each isomer was not clear at this stage, the major adduct **3** was converted to the known natural product (±)-aiphanol to establish its structure (see Scheme 1).



Scheme 1. Reagents and conditions: (a) THF, rt, 3 h [69% (**3**/**3′** 2:1)].

In this Letter, we wish to report the highly regioselective cycloaddition of *o*-quinones **4** and **2**, and conversion of the resulting adduct **5** to the antimalarial agent nitidanin (**6**), isolated from the wood of *Xanthoxylum nitidum* D.C. as a racemate[2] and from the heartwood of Indian *Santalum album* L. as a 7*S*,8*S* enantiomer (see Fig. 1).[3]

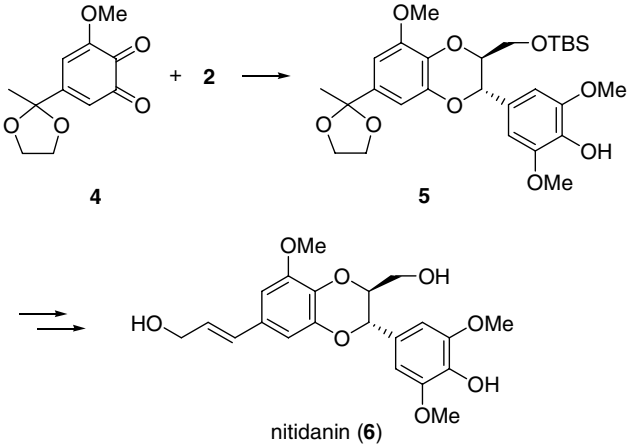


Figure 1. Regioselective cycloaddition of **4** and **2** to give adduct **5** and synthesis of (±)-nitidanin (**6**).

In addition, we describe two series of novel procedures for determination of the structure of **5** by chemical transformation. These transformations could be generally useful for discrimination of isomers such as **5** and

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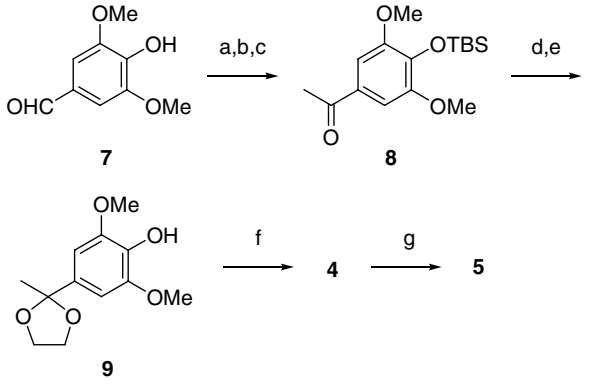
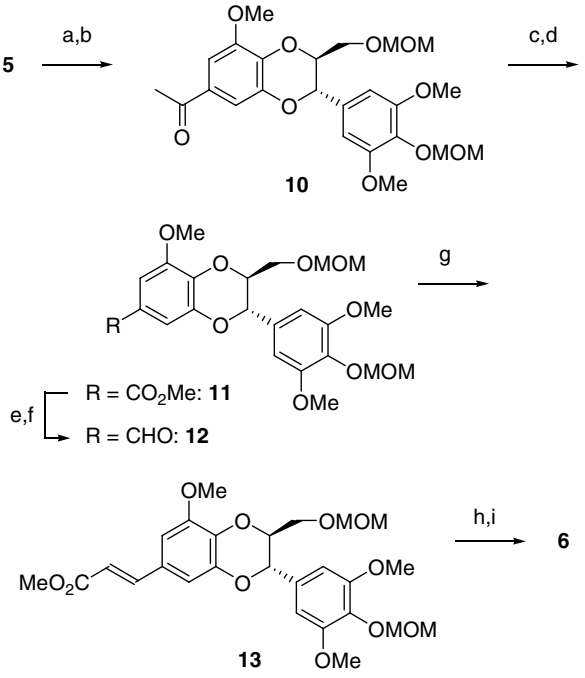
5′ (regioisomer of **5**), which is often difficult, even using modern 2D NMR techniques.

o-Quinone **4** was prepared from commercially available syringaldehyde (**7**) as shown in Scheme 2. Phenol **7** was protected by a TBS group, which was treated with methyl lithium followed by TPAP catalyzed oxidation to provide acetophenone **8** in 82% yield. Protection of ketone **8** and removal of the TBS ether gave phenol **9** in 83% yield. Oxidation of **9** with IBX[1,4,5] in DMSO afforded *o*-quinone **4**[6] in 82% yield. The *o*-quinone **4** was so stable that it could be stored without any decomposition for 1 year at −20 °C. Cycloaddition of **4** and **2** proceeded smoothly to give the adduct **5**[7] as a single isomer in 83% yield. The presence of a methoxy group in the quinone apparently increased the chemical yield and regioselectivity of the reaction. At this point, we could not clarify whether the structure of the adduct was **5** or **5′** by HMBC and NOESY experiments. To confirm the structure, we derivatized the adduct to **6**, the structure of which had been determined using advanced NMR techniques.



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, DMF, 0 °C to rt, 30 min (92%); (b) MeLi, THF, −78 °C, 1 h (94%); (c) TPAP, NMO, CH_2Cl_2, 0 °C to rt, 30 min (95%); (d) ethylene glycol, *p*TsOH, benzene, reflux, 3 h; (e) TBAF, THF, 0 °C to rt, 30 min (83% in two steps); (f) IBX, DMSO, rt, 30 min (82%); (g) **2**, THF, rt, 3 h (83%, single isomer).

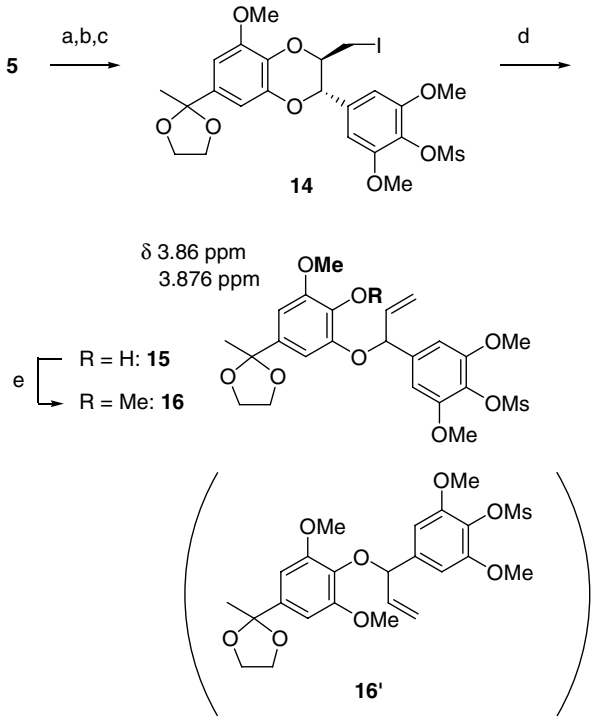
Since the structure of **5** could not be directly determined from our NMR experiments, we aimed to develop a simple method to identify **5** or **5′** (regioisomer of **5**) that did not depend on derivatization to a known compound. Our plan was based on selective cleavage of the 1,4-dioxane ring. The orientation of substituents around the benzene ring of the cleavage product would reflect the original substitution pattern around the 1,4-benzodioxane, and could easily be determined by NMR experiments (see Scheme 3).[10]



Scheme 3. Reagents and conditions: (a) AcCl, MeOH, 0 °C to rt, 1 h (80%); (b) MOMCl, *i*-Pr_2NEt, THF, rt, 1 h (quant.); (c) KI, H_2O, I_2, NaOH, DME, 0 °C, 30 min; (d) MeI, K_2CO_3, DMF, 0 °C to rt, 3 h (75% in two steps); (e) $LiAlH_4$, THF, 0 °C to rt, 30 min (75%); (f) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min; (g) $(MeO)_2P(O)CH_2CO_2Me$, *t*-BuOK, THF, 0 °C to rt, 30 min (73% in two steps); (h) AcCl, MeOH, 0 °C to rt, overnight; (i) DIBAL-H, CH_2Cl_2, −78 °C, 1 h (67% in two steps).

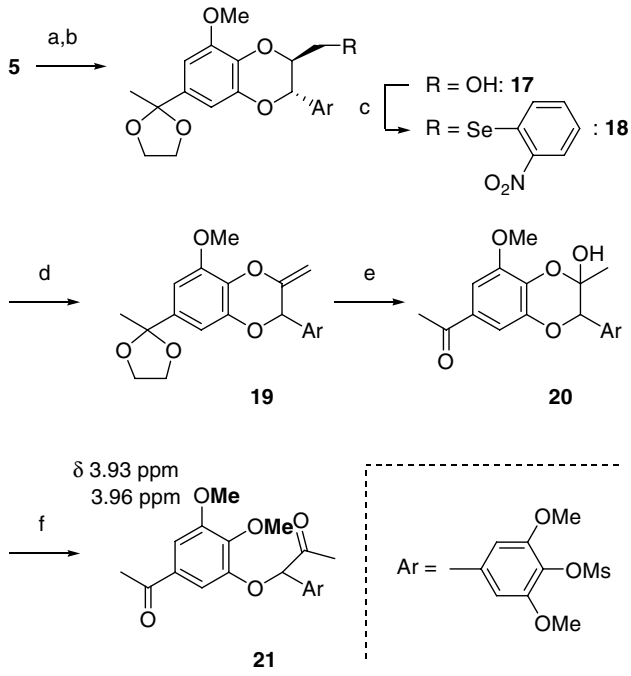
Removal of the protecting groups from **5** under acidic conditions in 88% yield, followed by protection of the hydroxyl group and phenol as MOM ether gave acetophenone **10** in quantitative yield. Acetophenone **10** was converted to methyl ester **11** by the iodoform reaction and subsequent esterification in 75% yield. Methyl ester **11** was transformed to benzaldehyde **12** by reduction using a $LiAlH_4$/Dess–Martin oxidation sequence. Treatment of **12** with trimethyl phosphonoacetate and potassium *t*-butoxide gave α,β-unsaturated ester **13** in 55% yield from **11**. Deprotection of all the MOM groups in **13** under acidic conditions and successive reduction with DIBAL-H provided **6** in 67% yield in two steps. ^1H and ^{13}C NMR spectra of the synthetic **6** were identical to those of the naturally isolated compound.[8,9] Thus, the total synthesis of (±)-nitidanin was accomplished in 10% overall yield from syringaldehyde (**4**) and the structure of intermediate **5** was confirmed.

The adduct **5** was subjected to the reactions shown in Scheme 4. Adduct **5** was converted to iodide **14** by sequential desilylation, mesylation and iodination in 76% in three steps. A 3-min treatment of **14** with *n*-BuLi at −78 °C induced cleavage of the 1,4-dioxane ring after halogen–metal exchange to afford the desired phenol **15**. A prolonged reaction time or the use of bromide instead of iodide decreased the yield substantially. Immediate methylation of **15** using methyl iodide and sodium hydride gave the desired methyl ether **16**[11] in 44% yield from **14**. ^1H NMR signals for **16** showed three singlets (δ 3.86, 3.876, 3.879 ppm), which indicated two nonequivalent methoxy groups on the benzene ring originating from *o*-quinone. If the isomer **5′** had been subjected to the same process, the product should be **16′**, which contains two equivalent methoxy groups on the benzene ring. Thus, the orientation of the side chain of the adduct was unambiguously established as **5**.



Scheme 4. Reagents and conditions: (a) TBAF, THF, rt, 2 h; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min (87% in two steps); (c) NaI, *i*-Pr_2NEt, DMF, 80 °C, 1 h (87%); (d) *n*-BuLi, THF, −78 °C, 3 min; (e) MeI, NaH, DMF, rt, 2 h (44% in two steps).

We turned to the alternative mild method shown in Scheme 5, since the ring cleavage reaction using *n*-BuLi was sometimes unsuccessful owing to decomposition of the product. After protection of phenol **5** as the mesylate, the TBS group was removed to give **17**. Primary alcohol **17** was converted to organoselenium compound **18** in 57% yield and oxidative elimination gave enol **19** in 94% yield, which was hydrolyzed under acidic conditions to hemiketal **20** in quantitative yield. Although cleavage of the hemiketal was troublesome by reduction and treatment with methylmagnesium bromide, the tautomeric phenol **20** could be directly methylated by treatment with methyl iodide and potassium carbonate to provide the desired methyl ether **21**[12] in 40% yield. ^1H NMR spectra of **21** indicated two non-equivalent methoxy groups on the benzene ring and again confirmed the structure of **5**.



Scheme 5. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min (60%); (b) TBAF, THF, rt, 1 h (quant.); (c) 4-nitrophenylselenyl cyanide, *n*-Bu_3P, THF, rt, overnight (57%); (d) *m*CPBA, CH_2Cl_2, 40 °C, overnight (94%); (e) 1 M HCl/THF (1:1), rt, overnight (quant.); (f) MeI, K_2CO_3, DMF, rt, 3 h (40%).

In conclusion, we developed a highly regioselective cycloaddition of *o*-quinone **4** and sinapyl alcohol unit **2** and achieved total synthesis of (±)-nitidanin (**6**) from the adduct **5**. In addition, we investigated two novel procedures for determination of the structure of **5** based on partial cleavage of the 1,4-benzodioxane ring. Application of these procedures to other systems and further studies on effect of substituents of the *o*-quinone to the regioselectivities are currently being conducted.

Acknowledgements

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6. *Spectral data for* **4**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 3H), 3.82 (s, 3H), 3.88 (dd, $J = 6.8$, 7.3 Hz, 2H), 4.08 (dd, $J = 6.8$, 7.3 Hz, 2H), 6.05 (s, 1H), 6.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 55.9, 64.7, 106.9, 117.1, 152.9, 175.0, 178.8.
7. *Spectral data for* **5**: ^1H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.64 (s, 3H), 3.60 (dd, $J = 3.3$, 12.6 Hz, 1H), 3.80–3.85 (m, 4H), 3.88 (s, 9H), 3.92–3.98 (m, 2H), 4.00–4.02 (m, 2H), 4.97 (d, $J = 7.2$ Hz, 1H), 5.61 (s, 1H), 6.66 (d, $J = 1.9$ Hz, 1H), 6.69 (s, 2H), 6.78 (d, $J = 1.9$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.7, −5.2, 14.2, 18.2, 25.8, 27.5, 56.2, 62.2, 64.4, 76.1, 78.3, 101.9, 104.1, 108.6, 127.7, 132.9, 134.5, 135.4, 135.8, 143.7, 147.0, 148.7.
8. *Spectral data for synthetic* **6**: ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (dd, $J = 3.2$, 12.7 Hz, 1H), 3.90 (s, 9H), 4.30 (dd,

$J = 1.2$, 4.6 Hz, 2H), 4.96 (d, $J = 8.24$ Hz, 1H), 5.62 (s, 1H), 6.25 (tt, $J = 5.6$, 16.0 Hz, 1H), 6.49 (dd, $J = 16.0$ Hz, 1H), 6.60 (d, $J = 1.8$ Hz, 1H), 6.67 (s, 2H), 6.69 (d, $J = 1.8$ Hz, 1H); ^{1}H NMR (500 MHz, $CD_3OD/CDCl_3$ 1:1): δ 3.54 (dd, $J = 4.4$, 12.7 Hz, 1H), 3.76 (dd, $J = 2.4$, 12.7 Hz, 1H), 3.89 (s, 3H), 3.93 (s, 6H), 4.06 (ddd, $J = 2.4$, 4.4, 8.3 Hz, 1H), 4.23 (dd, $J = 1.5$, 5.8 Hz, 2H), 4.90 (d, $J = 8.3$ Hz, 1H), 6.23 (dt, $J = 5.8$, 5.8, 16.1 Hz, 1H), 6.49 (dt, $J = 1.5$, 1.5, 16.1 Hz, 1H), 6.66 (d, $J = 1.8$ Hz, 1H), 6.68 (d, $J = 1.8$ Hz, 1H), 6.70 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1, 56.4, 61.5, 63.7, 76.8, 78.3, 102.6, 104.1, 108.8, 127.1, 127.3, 129.5, 130.9, 132.8, 135.3, 144.3, 147.3, 147.8; ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$ 1:1): δ 55.3, 55.4, 60.3, 62.0, 75.9, 78.2, 102.0, 103.9, 107.5, 126.3, 126.8, 129.1, 132.1, 135.2, 143.6, 147.4, 147.9.

9. There were some differences between the ^{1}H and ^{13}C NMR data for synthetic **6** in $CDCl_3$ and those reported in the literature, and we were thus skeptical about the structure of **5**. This is another reason why we started to develop a procedure to determine the structure of **5**. Good accordance of the NMR spectra for synthetic and natural nitidanin was obtained using a mixed solvent of $CDCl_3$/CD_3OD, as recommended in a personal communication with the authors of Ref. 2.
10. In more complicated cases, NOE experiments would be useful for determining the substitution pattern.
11. *Spectral data for* **16**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 3H), 3.28 (s, 3H), 3.53–3.59 (m, 1H), 3.63–3.66 (m, 1H), 3.86 (s, 3H), 3.876 (s, 3H), 3.879 (s, 6H), 3.90–3.97 (m, 2H), 5.28 (d, $J = 6.4$ Hz, 1H), 5.41 (d, $J = 17.2$ Hz, 1H), 5.63 (d, $J = 6.1$ Hz, 1H), 6.09 (ddd, $J = 6.1$, 6.4, 17.2 Hz, 1H), 6.67 (d, $J = 1.8$ Hz, 1H), 6.69 (d, $J = 1.8$ Hz, 1H), 6.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 39.8, 56.1, 56.3, 60.8, 64.4, 82.0, 103.1, 103.4, 107.3, 108.5, 117.3, 127.3, 137.3, 138.7, 138.9, 140.0, 150.6, 153.2, 153.4.
12. *Spectral data for* **21**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.50 (s, 3H), 3.30 (s, 3H), 3.91 (s, 6H), 3.93 (s, 3H), 3.95 (s, 3H), 5.54 (s, 1H), 6.81 (s, 2H), 7.12 (d, $J = 1.8$ Hz, 1H), 7.25 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 26.3, 39.9, 56.3, 56.4, 61.1, 86.6, 103.2, 106.9, 110.3, 128.3, 132.6, 134.5, 143.7, 150.4, 153.6, 153.7, 196.4, 204.6.