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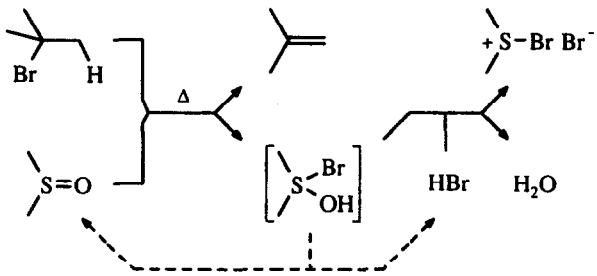
An Insight into the *t*-Butylbromide - Dimethyl Sulfoxide Reagent: A Novel Application in Lignan Total Synthesis.

David C. Harrowven* and Shelagh T. Dennison
Department of Chemistry, University of Wales, Bangor, Gwynedd, LL57 2UW.

Abstract : *A novel aromatisation sequence initiated by the t-butylbromide - dimethyl sulfoxide reagent is presented. The unprecedented conversion of the dithianes 1 and 3 to the aryl sulfides 6 and 7 has lead to the synthesis of the naturally occuring 9-deoxyarylnaphthalene lignans taiwanin C and 1,2,3,4-dehydrodeoxy-podophyllotoxin and gives a useful insight into the mechanism by which this unusual reagent acts.*

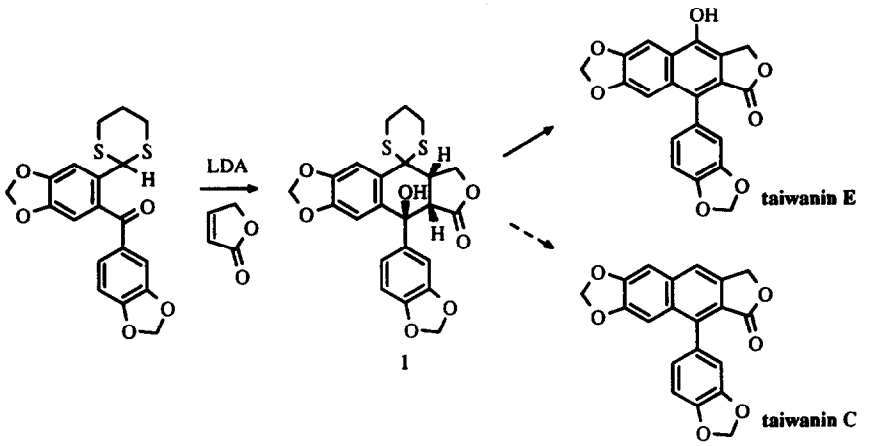
It is more than a decade since Marchelli *et al.* reported the surprising observation that sulfoxides could be deoxygenated simply through the action of *t*-butylbromide.[1] Their postulation that bromodimethyl-sulfonium bromide might be an intermediate in this reaction sequence soon lead to the development of a convenient new method for the *in situ* preparation of this useful material, namely the *t*-butylbromide - dimethyl sulfoxide reagent.[2] Yet surprisingly, in view of the seemingly mild, neutral and inexpensive nature of this reaction sequence, we have been unable to find any further reference to the use of this protocol in synthesis.[3] In this communication we wish to highlight a new application for this methodology and cast further light on the mechanism by which this reagent acts.



Scheme 1

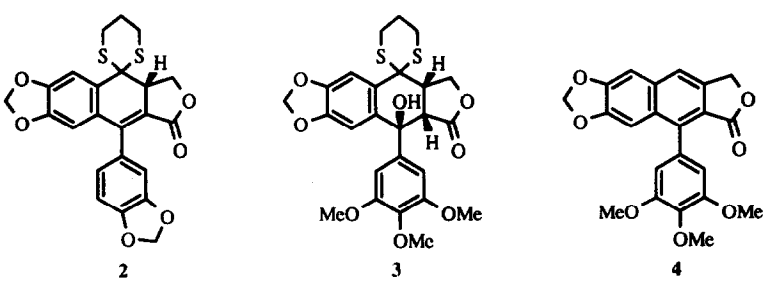
We first became interested in this reagent as part of our studies towards the *Podophyllum* lignans. Our recently disclosed entry to this family of natural products had used, as a central feature, a Michael initiated ring closue (MIRC type II) to affect the construction of the highly functionalised central ring system.[4] The MIRC adduct **1** was then elaborated to taiwanin E through sequential hydrolysis of the 1,3-dithiane and dehydration with tosic acid. To demonstrate the generality of this new protocol for the synthesis of the

arylnaphthalene lignans, we sought a convenient method for the conversion of the MIRC adduct into the 9-deoxy derivatives, also commonly found in nature, *e.g.* taiwanin C (Scheme 2). In principle this could be achieved by the aromatisation of the central ring, through sequential elimination of the benzylic alcohol and one of the benzylic sulfides, and subsequent reduction of the resultant aryl sulfide.



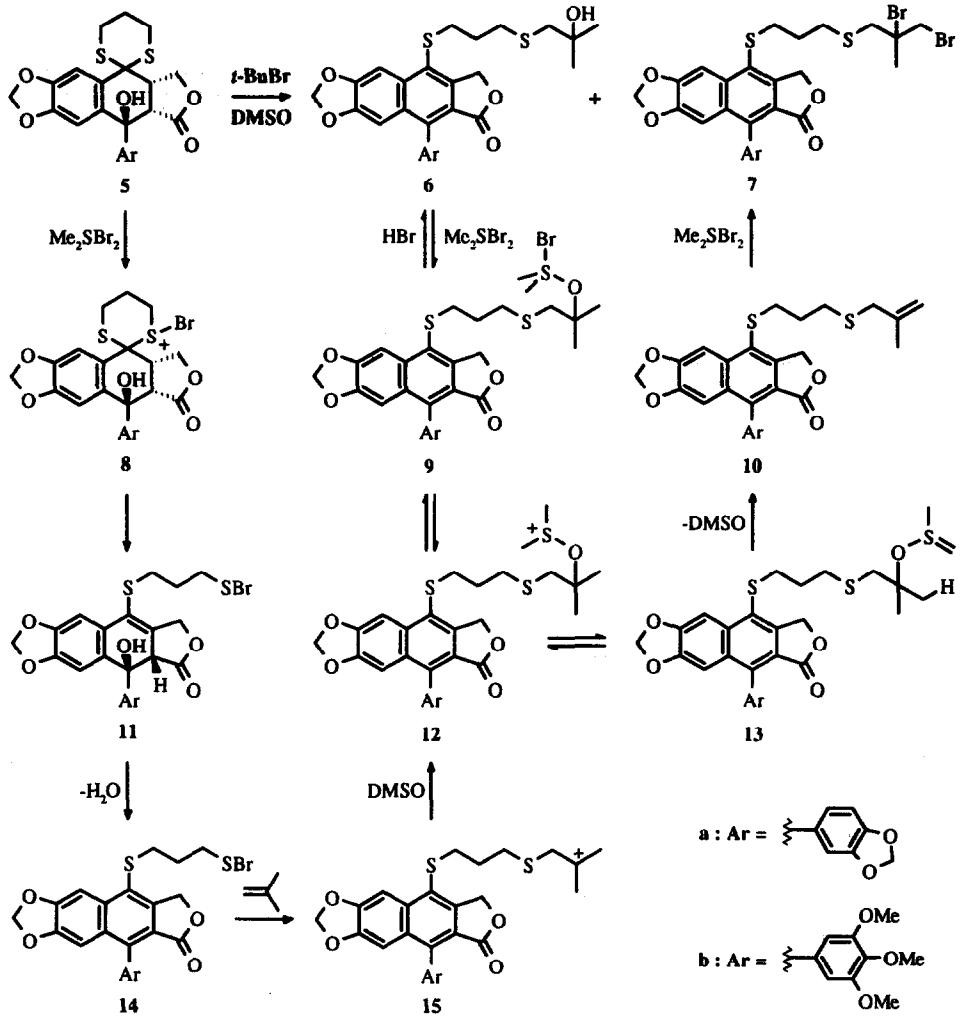
Scheme 2

To that end, our initial attempts to affect the direct aromatisation of the MIRC adduct **1**, using simple acid catalysis, provided only the product of dehydration **2**, albeit in near quantitative yield. However, activation of the dithiane by treatment of the adduct **1** with the t-butylbromide - dimethyl sulfoxide reagent smoothly affected the requisite sequential elimination, generating the aryl sulfide **6a** (81%) as a white crystaline solid.[5] Reduction of **6a** with Raney nickel then gave taiwanin C (83%), which was identical in all respects to the natural material.[6] In a similar fashion, warming a DMSO solution of the MIRC adduct **3** in the presence of *t*-BuBr gave a mixture of the aryl sulfides **6b** (69%) and **7b** (15%), which on exposure to Raney nickel furnished 1,2,3,4-dehydrodeoxypodophyllotoxin **4** (87%).[7]



The unprecedented conversion of the MIRC adducts to the aryl sulfides **6** and **7** presumably proceeds *via* the initial, *in situ* generation of 2-methylpropene and bromodimethylsulfonium bromide[2] (Scheme 1). Bromination of the dithiane **5** next initiates aromatisation by the sequential elimination of the activated sulfide and loss of water. The resultant bromide **14** and 2-methylpropene then combine to give the tertiary

carbocation **15**. Quenching this cation with DMSO then produces the adduct **12**, a precursor of the alcohol **6**. Alternatively, loss of a proton from **12**, elimination of DMSO then addition of bromine across the resulting olefin **10**, with bromodimethylsulfonyl bromide,[3b] provides the minor constituent **7** (Scheme 3).



Scheme 3

The role played by the *t*-butylbromide - dimethyl sulfoxide reagent, in initiating the sequential elimination of the MIRC adducts, was critical to this synthetic programme and further highlights the power of our Michael initiated ring closure protocol for the construction of highly substituted aromatic ring systems. Moreover, the novel cascade sequence that it mediates, viewed in conjunction with the findings of others,[2,8] provides a clearer insight into this curious reagent.

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References and Notes:

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2. Olah, G.A.; Mehrotra, A.K.; Narang, S.C.; *Synthesis*, **1982**, 151.
3. For other studies involving the use of bromodimethylsulphonium bromide see: **a.** Olah, G.A.; Ohannesian, L.; Arvanaghi, M.; *Synthesis.*, **1986**, 868. **b.** Chow, Y.L.; Bakker, B.H.; *Synthesis*, **1982**, 648. **c.** Chow, Y.L.; Bakker, B.H.; *Can. J. Chem.*, **1982**, *60*, 2268. **d.** Munavu, R.M.; *J. Org. Chem.*, **1980**, *45*, 3341. **e.** Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; Surya Prakash, G.K.; *Synthesis*, **1979**, 720. **f.** Olah, G.A.; Vankar, Y.D.; Arvanaghi, M.; *Tetrahedron Lett.*, **1979**, 3653. **g.** Gassman, P.G.; van Bergen, T.J.; Gruetzmacher, G.; *J. Am. Chem. Soc.*, **1973**, *95*, 6508.
4. Harrowven, D.C.; *Tetrahedron Lett.*, **1991**, *32*, 3735.
5. All new compounds gave satisfactory analytical and spectroscopic characteristics e.g. For **6a** : white solid; m.p. (chloroform/hexane) 233-236°C dec.; FT-IR ($CHCl_3$) υ_{max} 2940m, 2910m, 2840m, 1760s, 1465m, 1360m and 1130cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 332 (9100) and 350 (6100) nm; ^{1}H NMR (250MHz, $CDCl_3$) δ_H 7.97 (1H, s, Ar*H*), 7.15 (1H, s, Ar*H*), 6.97 (1H, d, *J* = 7Hz, Ar*H*), 6.79 (1H, s, Ar*H*), 6.78 (1H, d, *J* = 7Hz, Ar*H*), 6.13 (2H, s, OCH_2O), 6.08 (2H, ab, OCH_2O), 5.42 (2H, s, OCH_2), 3.02 (2H, t, *J* = 7Hz, SCH_2), 2.98 (1H, d, *J* = 14Hz, SC*H*HC), 2.91 (2H, t, *J* = 7Hz, SCH_2), 2.72 (1H, d, *J* = 14Hz, SCH*H*C), 2.11 (2H, quin., *J* = 7Hz, $CH_2CH_2CH_2$) and 1.21 (6H, s, 2xCH_3) p.p.m.; ^{13}C NMR (61.3MHz, $CDCl_3$) 169.5 (s), 152.0 (s), 148.5 (s), 147.7 (s), 147.4 (s), 145.7 (s), 141.5 (s), 137.0 (s), 131.4 (s), 127.6 (s), 123.3 (d{&s?}), 118.8 (s), 110.2 (d), 108.1 (d), 104.5 (d), 102.0 (t), 101.5 (d), 101.1 (t), 70.3 (s), 68.3 (t), 51.9 (t), 34.4 (t), 31.7 (t), 30.3 (t) and 29.4 (2xq); $^m/_z$ (EI) 525 ([M-H]$^+$, 1%), 509 ([M-OH]$^+$, 4), 453 (10), 420 (44), 380 (100) 321 (40), 319 (33) and 293 (80) amu. For **7b** : white solid; m.p. (ether/hexane) 180°C dec.; FT-IR ($CHCl_3$) υ_{max} 2940m, 2840m, 1766s, 1585m, 1465m, and 1130m cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 263 (32000), 330 (9500) and 353 (5000) nm; ^{1}H NMR (270MHz, $CDCl_3$) δ_H 7.94 (1H, s, Ar*H*), 7.07 (1H, s, Ar*H*), 6.46 (2H, s, 2xAr*H*), 6.06 (2H, s, OCH_2O), 5.37 (2H, s, OCH_2), 4.00 (1H, d, *J* = 10.2Hz, C*H*HBr), 3.89 (3H, s, O*Me*), 3.77 (6H, s, 2xO*Me*), 3.74 (1H, d, *J* = 10.2Hz, CH*H*Br), 3.10 (2H, ABq, SCH_2C), 2.88 (2H, t, *J* = 7.1Hz, SCH_2CH$_2$), 2.73 (2H, t, *J* = 7.1Hz, SCH_2CH$_2$), 1.82 (3H, s, CH_3) and 1.78 (2H, quin, *J* = $CH_2CH_2CH_2$) p.p.m.; ^{13}C NMR (67.8MHz, $CDCl_3$) δ_C 169.51 (s), 152.97 (2xs), 151.07 (s), 148.70 (s), 145.51 (s), 137.88 (s), 136.64 (s), 131.34 (s), 129.90 (s), 123.27 (s), 118.89 (s), 107.12 (d), 104.67 (d), 102.10 (t), 101.82 (d), 68.63 (t), 65.59 (s), 61.01 (q), 56.14 (2zq), 44.85 (t), 41.46 (t), 34.31 (t), 32.67 (t), 30.03 (q) and 29.28 (t) p.p.m.; $^m/_z$ (FAB) found 715 (2.6%, M$^+$+3), 714 (3.8, M$^+$+2), 713 (1.3, M$^+$+1), 712 (0.8, M$^+$) and 499 (3.0) amu.
6. Taiwanin C was first isolated from plant sources as a constituent of the heartwood of *Taiwania cryptomerioides*; Lin, Y.-T.; Lo, T.-B.; Shih, E.-H.; *J. Chin. Chem. Soc., Ser. II*, **1955**, *2*, 87; *Chem. Abstr.*, *50*, 7086. Our synthetic sample exhibited : white solid; m.p. (chloroform/hexane) 273-276°C (lit. 267-270°C); FT-IR ($CHCl_3$) υ_{max} 3020s, 2985m, 1760m, 1520m, 1465m, 1045s and 930s cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 254 (35000), 261 (38000), 291 (9300), 302 (8900) and 347 (4200) nm; ^{1}H NMR (250MHz, $CDCl_3$) δ_H 7.71 (1H, s, Ar*H*), 7.21 (1H, s, Ar*H*), 7.12 (1H, s, Ar*H*), 6.97 (1H, d, *J* = 7Hz, Ar*H*), 6.81 (1H, s, Ar*H*), 6.79 (1H, d, *J* = 7Hz, Ar*H*), 6.09 (2H, s, OCH_2O), 6.09 (2H, ab, OCH_2O) and 5.38 (2H, s, OCH_2) p.p.m.; $^m/_z$ (EI) 348 (100%, M$^+$), 319 (9, [M-CHO]$^+$), 289 (16), 261 (26) and 233 (17) amu.
7. 1,2,3,4-Dehydrodeoxypodophyllotoxin was first isolated from plant sources as a minor constituent of the seeds of *Hernandia ovigera* L. (Hernandiaceae); Yanaguchi, H.; Arimoto, M.; Tanoguchi, M.; Ishida, T.; Inoue, M.; *Chem. Pharm. Bull.*, **1982**, *30*, 3212. Our synthetic sample exhibited : white solid; m.p. (chloroform/hexane) 274-276°C (lit. 276-278°C); FT-IR ($CHCl_3$) υ_{max} 2930m, 2855m, 1762vs, 1585m, 1465s, 1130s and 910s cm^{-1}; UV λ_{max} (ε) ($CHCl_3$) 258 (38000), 309 (9600) and 351 (4900) nm; ^{1}H NMR (270MHz, $CDCl_3$) δ_H 7.71 (1H, s, Ar*H*), 7.21 (1H, s, Ar*H*), 7.11 (1H, s, Ar*H*), 6.55 (2H, s, 2xAr*H*), 6.09 (2H, s, OCH_2O), 5.39 (2H, s, OCH_2), 3.96 (3H, s, O*Me*) and 3.84 (6H, s, 2xO*Me*) p.p.m.; ^{13}C NMR (67.8MHz, $CDCl_3$) δ_C 169.61 (s), 152.92 (2xs), 149.96 (s), 148.66 (s), 140.38 (s), 137.73 (s), 134.57 (s), 130.30 (2xs), 107.21 (2xd), 103.70 (d), 103.61 (d), 101.82 (t), 67.96 (t), 60.97 (q) and 56.10 (2xq) p.p.m.; $^m/_z$ (FAB) found (EI) found 394 (M$^+$, 100%) and 379 (31) amu.
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