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Toward a total synthesis of stigmatellin; an unproductive *C-1′–C-2′* disconnection

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Abstract

Although the lithio derivative of the dimethylchromone **6c** could be condensed with reactive organic electrophilic species and iodine to give, respectively, homologated at *C-1′* (stigmatellin numeration) chromones and the iodide **6a**, it proved impossible to convert efficiently either **6a** or **6c** into stigmatellin **1a** by an anionic alkylation process.

Isolated a few years ago by Höfle from a culture of the gliding bacteria *Stigmatella auriantaca* as a mixture of the two stereomers **1a** and **1b**,[1] stigmatellin **1** has proved to be a potent inhibitor of the photosynthetic system. It is, accordingly, a useful tool for studying relevant electron-transfer phenomena.[2]

Although most of the structural features of **1a** and **1b** were determined earlier,[1] it was not until recently that both the relative and absolute configurations of their four stereogenic centres have been ascertained by identification of a degradation product of **1a** to an authentic, synthetic, sample.[3] To date, no total synthesis of these compounds has been claimed.

With the aim to synthesise stigmatellin **1a** according to the indicated plan, we first examined the possibility to generate the fragment **2a** from the aldehyde **3a**, which is easily accessible from the sulfide **4**, via **3b**, by means inter alia of a modified Kiliani–Fischer methodology[4] (Scheme 1). Condensation of **3a** with the dienylsulfone ***E*-5** in the conditions of the Julia–Paris–Kocienski (JPK) reaction and subsequent oxidation of the expected sulfide **2b** would have provided the trienyl sulfone **2a**. Alkylation of **2a** by the iodochromone **6a**, followed by hydrogenolysis of the sulfonyl group would have then delivered the target molecule.

Although, somewhat unexpectedly, this plan proved to be of little value at an advanced stage of this synthesis, a few interesting points emerged from this exploratory study, especially those which concern the elaboration of the chromone derivative **6c**. These results are, accordingly, reported herein, whereas a more valuable synthetic scheme is presented in the accompanying letter.[5]

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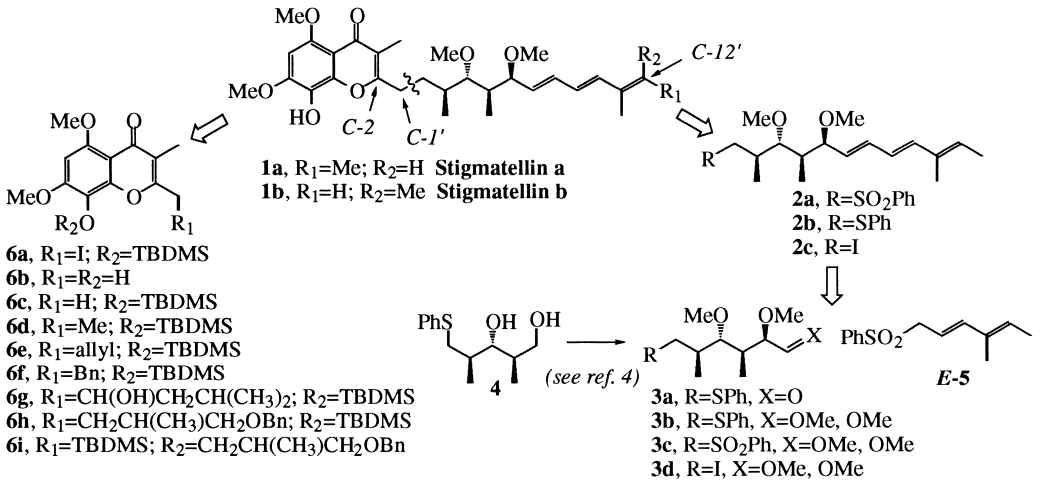
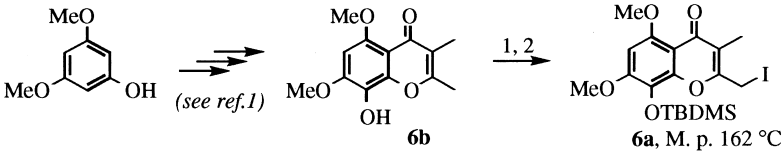


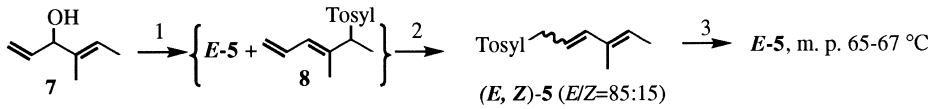
Scheme 1.

The required iodide **6a** was prepared by starting from commercial 3,5-dimethoxyphenol, which was first converted into the chromone **6b** as described.[1] Due to the sensitivity of **6b** to air, especially in basic media, its free phenol functionality was immediately protected by treatment with TBDMSCl and imidazole. The stable chromone derivative **6c** thus obtained was then reacted sequentially with LDA and NIS to give, after recrystallisation, the iodo derivative **6a** as yellow prisms (37% overall, from **6b**) (Scheme 2).



Scheme 2. Reagents and conditions: (1) TBDMSCl (2.5 equiv.), imidazole (2.5 equiv.); DMF, rt, 15 h (73%); (2) LDA (1 equiv.), THF; –78°C, 1 h, then NIS (1.5 equiv.), –78°C, 2 h (37% overall, from **6b**)

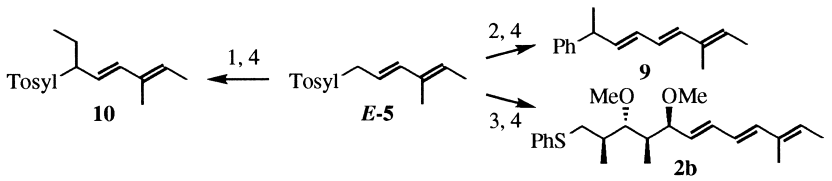
Next, the preparation of the dienyl sulfone ***E*-5** was examined. Condensation of the bis-allylic alcohol **7** with *p*-toluenesulfinyl chloride afforded a 2:3 mixture (NMR) of, respectively, the sulfone ***E*-5** and **8** in high yield (92%) (Scheme 3). By treatment with excess *p*-toluenesulfinic acid in $CHCl_3$,[6] this mixture evoluted to give, after a few hours, an oily product which was mainly constituted of the desired sulfone ***E*-5**, admixed, however, with its *Z*-isomer ***Z*-5** (*E*:*Z* = 85:15, by NMR). Chromatography of this product on silica gel and recrystallisation of the purest fractions then furnished the pure sulfone ***E*-5a** (43%).



Scheme 3. Reagents and conditions: (1) *p*-toluenesulfinyl chloride (1.5 equiv.), NEt_3 (1.6 equiv.), CH_2Cl_2; –78°C, 5 min (92%); (2) *p*-toluenesulfinic acid (2.5 equiv.), $CHCl_3$; rt, 12 h; (3) column chromatography on silica gel (CH_2Cl_2/hexane), then recrystallisation from ether/hexane (43%)

The possibility to engage ***E*-5** in a JPK coupling was tested by treating this sulfone with butyllithium in THF at low temperature. The thus-formed lithio derivative was reacted, on the one hand, with acetaldehyde, and on the other hand, with 2-phenylpropanal. In both cases, this condensation step was followed by in situ addition of Ac_2O and DMAP, then reduction of the resulting mixture of diastereomeric acetoxy-sulfones by sodium amalgam in MeOH, diluted with a phosphate buffer, at low temperature.

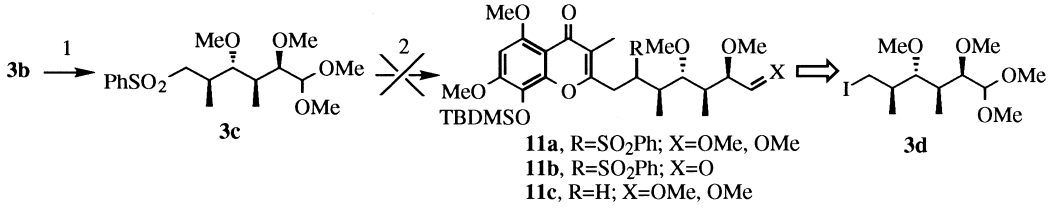
Surprisingly, whereas 2-phenylpropanal afforded the triene **9** as expected, the dienylsulfone **10**[7] was the only product isolated in the experiment with acetaldehyde (Scheme 4). Notwithstanding this divergence, a similar JPK sequence was applied to the aldehyde **3a**. In this case, the reduction step proceeded very slowly, requiring repeated additions of both HgNa and the phosphate buffer to go to completion. Nevertheless, the pure (NMR, UV) trienyl sulfide **2b** was isolated in a fairly good yield (70% overall, from **3a**).



Scheme 4. Reagents and conditions: (1) 1.2 M (in hexane) *n*-BuLi (1.05 equiv.), THF; –78 to 35°C, 15 min, then –78°C, 0.5 h, then acetaldehyde (1.3 equiv.); –78 to –20°C, 15 min; (2) same conditions as in (1) with 2-phenylpropanal; (3) same conditions as in (1) with the aldehyde **3a**; (4) (i) Ac_2O (2.1 equiv.), DMAP (0.11 equiv.), rt, 1 h; (ii) 6% HgNa (400 mg/mmol, three times), $HNa_2PO_4{\cdot}12H_2O$ (3×4 equiv.), MeOH; –20°C, 5–7 h

Attempted oxidation of this sulfide in mild conditions (n-Bu_4NIO_4) proved inefficient. Due to the sensitivity of the trienyl residue in **2b** (or **2a**), only traces of **2a** could be characterised and after several unsuccessful experiments with various oxidising reagents, it became clear that our initial plan needed some adjustment.

The alkylation of the sulfone **3c**, which formed by oxidation of **3b** with oxone in a buffer media (80%), by the iodochromone **6a** was then considered, our hope being that the aldehyde **11b**, which should form by hydrolysis of the expected acetal **11a**, would suffer a JPK[8] condensation with the sulfone ***E*-5** (Scheme 5). In the event, a treatment with HgNa as above would have then provided the *O*-TBDMS derivative of **1a**.



Scheme 5. Reagents and conditions: (1) oxone (5 equiv.), pH 8–9 phosphate buffer, MeOH; 0°C, 4 h (80%; (2) *n*-BuLi (1.3 equiv.), HMPT (1.3 equiv.), THF; –78°C to rt

This plan proved no more efficient than the preceding one, however, although **3c** could indeed be anionised by treatment with butyllithium, as evidenced by quenching with either D_2O or allyl bromide, treatment of the thus-formed lithio derivative by the iodide **6a** did not provide usefully

the desired sulfone **11a**: due presumably to exceeding acidity of the CH_2 group at position 2 of the chromone nucleus in **11a**, extensive elimination of the sulfonyl group occurred and, at best, only trace amounts of **11a** could be detected at low conversion.

Another possibility was to condense the iodide **3d** with the lithio derivative of **6c** (or the related organocopper and cerium species) to form **11c**: hydrolysis of this acetal, followed by a JPK condensation with ***E*-5a** and desilylation would have then delivered **1a**. The validity of this scheme was tested by condensing anionised **6c** with various reagents (Table 1).[9]

Table 1
Condensation of anionised **6c** with organic electrophines

Entry	Reagents	Base	Product (% Yield)
1	CH_3I	LDA (1.2 eq.), HMPA (2eq.)	**6d** (80 %)
2	CH_2=CH-CH_2Br	"	**6e** (75 %)
3	$PhCH_2Br$	"	**6f** (63 %)
4	$(CH_3)_2$CH-CH_2CHO	LDA (1.2 eq.)	**6g** (90 %)
5	$BnOCH_2CH(CH_3)CH_2I$	LiHMDS (1.2 eq.), HMPA (4 eq.)	**6h** (4 %), **6i** (45 %)

As can be seen, whereas the more electrophilic reagents efficiently gave the expected product (Entries 1–4), a γ-oxygenated iodide modelling accurately the iodide **3d** gave only traces of the desired product **6h**, the main product being the *O*-alkylation product **6i** (Entry 5), a result not improved by using the corresponding triflate or by first reacting the lithio derivative of **6c** with either CuI or $CeCl_3$. Owing to these consecutive difficulties, the initial plan and its various variations were definitively thrown out.

In conclusion, a few positive points emerged from this study as, for instance, the possibility to generate the triene residue of stigmatellin by using an olefination process. Additionally, clean homologation at *C-1′* of a 2-methylchromone has been realised in several cases.[10] However, all attempts to elaborate the chromone **6c** toward the stigmatellin molecule **1a** proved to be not very efficient and it now seems clear to us that any viable strategy for synthesizing stigmatellin **1a** should comprise an early appendage of an advanced fragment of the *C-2* side chain to a suitable precursor of the heterocyclic part of **1a**, prior to the generation of the chromone ring system. Such an approach is described in the accompanying Letter.[5]

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7. Presumably formed by basic elimination of an acetate ion in the transcient acetoxysulfone, followed by hydrogenation of the thus-formed vinylsulfone residue.
8. *Protocol for the JPK olefination process* (all operations performed in an argon atmosphere): To a cooled (ca. –78°C) solution of the sulfone ***E*-5** (25.1 mg, 0.1 mmol) in THF was added a 1.2 M solution of *n*-BuLi in hexane (0.1 ml). The resulting orange–red mixture was warmed up to –45°C for 5 min, then cooled to –78°C. The

aldehyde **3a** (14.9 mg, 0.05 mmol), diluted with THF (0.6 ml), was then added, which induced a slight decolouration. Stirring was pursued 1 hour at –78°C, then 5 min at –20°C, after that DMAP (0.06 mg) and Ac_2O (0.01 ml) were added sequentially. After 45 min stirring at rt, the resulting thick mixture was diluted with ether (10 ml), and water (9 ml). Extraction with ether (4×2 ml) of the aqueous phase was followed by washing of the pooled organic layers with brine until neutral. After drying ($MgSO_4$), the solvents were evaporated to give a yellow oil (52.9 mg) which was immediately diluted with methanol (2 ml). To the resulting solution, HNa_2PO_4 (52 mg) and 6% NaHg (170 mg) were added sequentially, the addition of both reagent (same amount) being repeated twice every 2 hours. Water (10 ml) and hexane (10 ml) were then added and the resulting mixture was stirred for 0.5 hour. The aqueous phase was further extracted with ether (3×2 ml), the pooled organic extracts then being washed with brine, and dried ($MgSO_4$). Evaporation of the solvents, followed by filtration of the residue on Florisil (pentane) afforded the sulfide **2b** (13.1 mg, 70%, from **3a**) as a colourless oil. ^{13}C NMR: 10.4, 12.1, 14.8, 15.5, 36.3, 38.1, 40.4, 55.8, 61.2, 83.5, 84, 125.1, 125.9, 128.2, 128.9, 130.7, 135.2, 138.2, 134.6; UV (CH_2Cl_2): 260.8 (0.85), 271.3 (0.9), 282.4 (0.69) (in bracket: ee values).

9. *Typical experimental procedure*: To a cooled (ca. –78°C) solution of the chromone **6c** in THF (1.5 ml/mmol) was added, under an argon atmosphere, a 1 M solution of LDA (1.5 equiv.) in THF. After 1 hour stirring, the electrophilic reagent (see Table 1 in the text, 1.5 equiv.) and HMPA (2 equiv.) were added sequentially. This mixture was stirred at rt for 15 min, then diluted with ether (10 ml/mmol), and 10% $NaHCO_3$ (10 ml/mmol). After a further 2 hours stirring, the aqueous layer was extracted with ether (2×10 ml/mmol) and the pooled organic extracts were washed with brine (5×10 ml/mmol), and dried (K_2CO_3). Evaporation of the solvents was followed by chromatography of the residue on 60 silica gel (AcOEt) to afford the pure chromone.
10. *Selected data*: compound ***E-5***: m.p. 65–67°C (ether/hexane, 1.49 (d, J = 7.14 Hz, 3H), 1.81 (d, J = 1 Hz, 3H), 2.42 (s, 3H), 3.65 (q, J = 7.14 Hz, 1H), 5.01–5.13 (m, 2H), 5.69 (dq, J = 10.5, 1 Hz, 1H), 6.48 (td, J = 16.5, 10.5 Hz, 1H), 7.29 (m, 2H), 7.67 (m, 2H); ^{13}C NMR: 12, 14, 21.7, 60.7, 111.4, 128.5, 129.7, 133.7, 135.8, 144, 144.6; compound **6a**: m.p. 162°C (diisopropyl ether); compound **6c**: m.p. 108°C (hexane); compound **6d**: ^1H NMR: 0.13 (s, 6H), 1.02 (s, 9H), 1.25 (t, J = 7.5 Hz, 3H), 1.95 (s, 3H), 2.6 (q, J = 7.5 Hz, 2H), 3.87 (s, 3H), 3.89 (s, 3H), 6.35 (s, 1H); ^{13}C NMR: –4.4, 9.5, 11.8, 18.7, 25.4, 25.8, 55.7, 56.9, 92.4, 108.5, 116.2, 126, 150.1, 153.5, 154, 163.6, 177.9; compound **6e**: ^1H NMR: 0.14 (s, 6H), 1.02 (s, 9H), 1.96 (s, 3H), 2.45 (dd, J = 7.9, 6.9 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 5.08 (m, 2H), 5.78 (m, 1H), 6.35 (s, 1H); ^{13}C NMR: –4.4, 9.7, 18.7, 25.6, 31.5, 31.6, 55.7, 56.7, 92.3, 108.5, 116.1, 117.1, 126, 136.5, 149, 153.5, 154, 161.5, 185.9; compound **6f**: ^1H NMR: 0.19 (s, 3H), 1.09 (s, 9H), 1.85 (s, 3H), 2.87–3 (m, 4H), 3.92 (s, 3H), 3.94 (s, 3H), 6.4 (s, 1H), 7.15–7.32 (m, 5H); ^{13}C NMR: –4.3, 9.7, 18.8, 25.9, 33.7, 34.3, 55.7, 56.7, 92.3, 108.3, 117.4, 126.5, 127.3, 128.4, 140.4, 149.6, 153.6, 154.1, 161.1, 191.2; compound **6g**: ^1H NMR: 0.08 (s, 3H), 0.15 (s, 3H), 1.03 (s, 15H), 1.8 (m, 1H), 1.98 (s, 3H), 2.69 (m, 2H), 3.4 (s, 1H, O*H*), 3.85 (s, 3H), 3.86 (m, 2H), 3.87 (s, 3H), 6.18 (s, 1H); ^{13}C NMR: –4.5, 10.2, 18, 18.7, 19.1, 25.94, 34.2, 37.7, 55.1, 56, 74.1, 91.1, 107.5, 118.8, 127, 149.8, 152.9, 153.7, 160.8, 177.4. ^1H and ^{13}C NMR in $CDCl_3$ at 200 and 50 MHz, respectively.