Pergamon

Tetrahedron Letters 41 (2000) 5501–5505

TETRAHEDRON LETTERS

Toward a total synthesis of stigmatellin; obtention of an advanced fragment from gallic acid

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Received 31 March 2000; accepted 12 May 2000

Abstract

Treatment by a base, then an acid, of the ester **3**, which was prepared by starting from gallic acid **7a**, afforded the chromone **6c**, whose Swern oxidation, followed by condensation of the resulting aldehyde **6a** with the trienyl lithium derivative **13b** and methyl iodide, furnished products isomeric with, but not strictly identical to, an authentic sample of *O*-benzyl stigmatellin **1c**. © 2000 Elsevier Science Ltd. All rights reserved.

As explained in the preceding letter,[1] attempts to synthesise stigmatellin **1a** by homologating the chromone **2a** at *C-1′* (stigmatellin numeration) proved to be very useful and another plan based on the generation at a later stage of the synthesis of the chromone residue was examined.

Our hope was, as shown in Scheme 1, that the compound **3**, which should form by condensing the monoprotected derivative **4b** of the bis-phenol **4a** with the acid **5a**, would afford the chromone **6b** in basic conditions. In the event, the troublesome *C-1′–C-2′* connection would have been avoided. Additionally, exchange of the benzyl group of **6b** to a more accurate protection, followed by deprotection and oxidation of its primary alcohol functionality would have provided an aldehyde parent of **6a** potentially convertible into the target stigmatellin molecule. Although the last step leading from **6** to **1** still needs some improvement, we are pleased to report herein that this second strategy proved to be viable, permitting us to generate the stigmatellin skeleton.

The first problem we had to solve was to prepare, then to protect selectively, the required propiophenone **4a**. Although this ketone could previously be obtained by starting from the expensive 3,5-dimethoxyphenol as described,[2] it soon became manifest that the pursuit of this synthetic endeavour would necessitate disposing of large amounts of this crucial intermediate and, accordingly, another way, i.e. starting from the cheaper, readily available, gallic acid **7a**, was explored.

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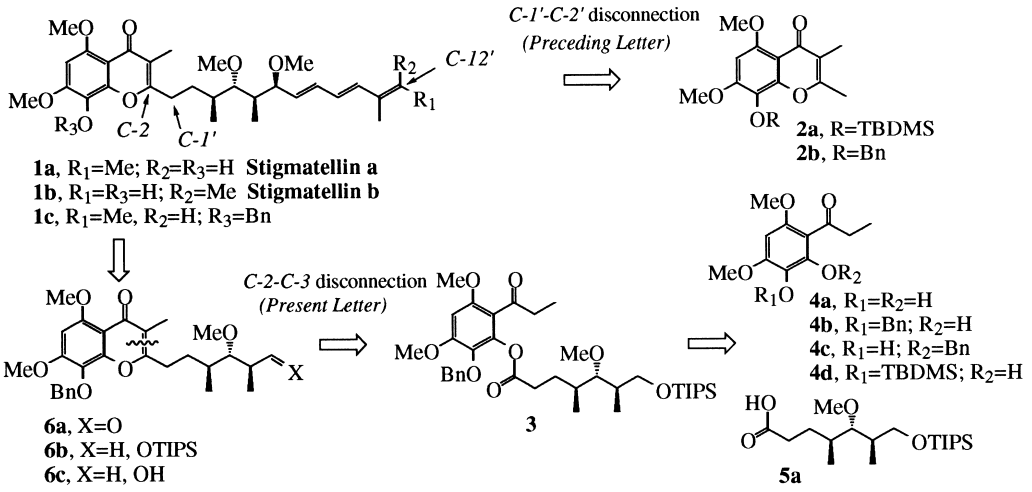
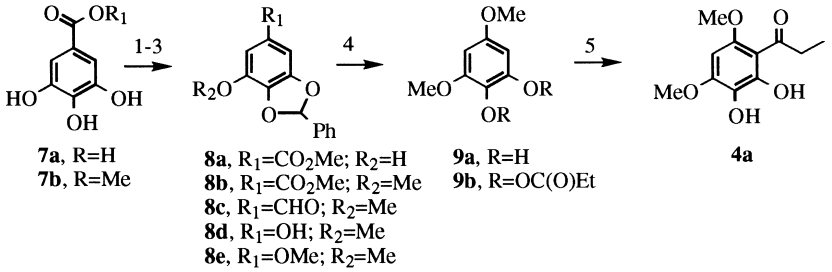
PII: S0040-4039(00)00812-1



Scheme 1.

As indicated, its methyl ester **7b** was first condensed with *a*,*a*-dichlorotoluene in basic conditions[3a] to afford the acetal **8a** (32%), besides unreacted **7b**. Subsequent treatment of **8a** with methyl iodide and KH furnished **8b** (Scheme 2).



Scheme 2. Reagents and conditions: (1) (i) $PhCHCl_2$ (1 equiv.), K_2CO_3 (3 equiv.), DMF (1 ml/mmol); 80°C, 3 days (32%); (ii) MeI (2 equiv.), K_2CO_3 (3 equiv.), DMF (3 ml/mmol); 0°C, 3 h (100%); (2) (i) 1 M (in CH_2Cl_2) DIBAH (2.4 equiv.), CH_2Cl_2 (8 ml/mmol); –78°C, 3 h (97%); (ii) PCC (1.5 equiv.), CH_2Cl_2 (2.5 ml/mmol); rt, 2 h, then filtration on Celite (76%); (3) (i) 30% aqueous H_2O_2 (0.5 ml/mmol, 4 equiv.), $(PhSe)_2$ (0.1 equiv.), CH_2Cl_2 (2 ml/mmol); rt, 2 days; (ii) KOH (2.5 equiv.), MeOH (0.7 ml/mmol); rt, 30 min; (iii) MeI (2 equiv.), DMSO (2.5 ml/mmol), KOH (4 equiv.); rt, 3 h (80% overall, from **8c**); (4) (i) 20% $Pd(OH)_2/C$ (25 mg/mmol), H_2 (normal pressure), MeOH (25 ml/mmol); rt, 18 h (100%); (ii) EtCOCl (2 equiv.), pyridine (2 equiv.), ether (1 ml/mmol); rt, 4 h (98%); (5) (i) $AlCl_3$ (2 equiv.), CH_2Cl_2 (4 ml/mmol); rt, 3 h; (ii) 6N aqueous HCl (1 ml/mmol), MeOH (4 ml/mmol); reflux, 0.5 h (94%)

Next, treatment of the aldehyde **8c**, best prepared in two steps by full reduction of the ester **8b** with DIBA-H, followed by oxidation of the resulting alcohol with PCC, by hydrogen peroxide in the presence of a catalytic amount of phenylselenic acid,[3b] followed by hydrolysis with KOH of the formate, thus formed furnished the air-sensitive phenolic compound **8d**, which was immediately converted into the stable methylether **8e** (ICH_3, KOH). Interestingly, several grams of this key intermediate could be obtained this way without any noticeable difficulties.

The final conversion of **8e** into **4a** was executed by first removing the benzylidene group of **8e** by hydrogenation, then, in analogy with the literature,[2] by fully esterifying the resulting bis-phenol

9a by treatment with excess propionic anhydride. Subsequent $AlCl_3$-induced Fries rearrangement of the resulting bis-propionate **9b**, followed by hydrolysis, delivered the propiophenone **4a** in an interesting 92% overall yield (from **9a**).

Selective benzylation of the more reactive (i.e. *meta* to the keto group) phenolic functionality of **4a** to form **4b**, preferred to other derivatives (e.g. **4d**) owing to its good resistance to the heterocyclisation conditions (vide infra), proved not so straightforward (Table 1).

Table 1

4a —(Base, RX)→ **4b-d**

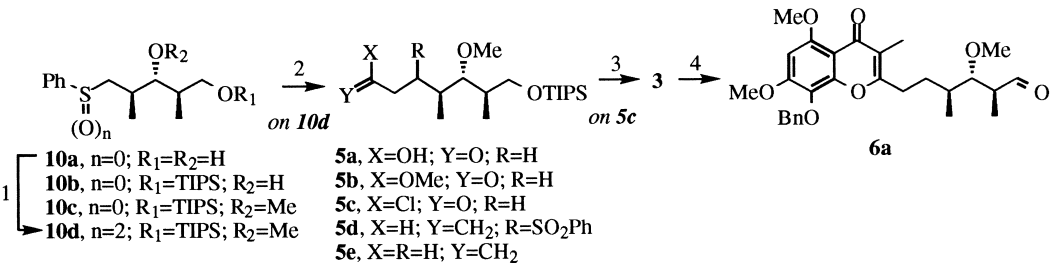
RX (eq.)		Base (eq.), solvent	Products (Yield)*
BnBr	(1.1)	NaH (1.1), THF	**4b** (43%)
"	"	Hünig base (1.1), CH_2Cl_2	**4b** (60%), **4c** (9%)
"	(4)	"	**4b** (71%)
TBDMSCl	(1.5)	Imidazole (1.5), DMF	**4d** (95%)

** All reactions were run for 1day, at room t.*

Hence, condensation of benzyl bromide with the sodium salt which formed by treating **4a** with NaH in THF indeed gave the monobenzyl derivative **4b** but in a deceptively low yield (43%), not improved by increasing the reaction time, in which case the formation of various side products occurred (TLC). By contrast, the *O*-TBDMS derivative **4d** was formed quantitatively by reacting **4a** with TBDMSCl and imidazole (Entry 4). The preceding benzylation was, accordingly, attempted in the presence of an amine (Hünig base), the bromide being still used in stoichiometry. The reaction proceeded slowly, affording after 1 day the desired benzyl derivative **4b** in moderate yield (60%), besides its regioisomer **4c** (9%). Given the slow rate at which this reaction occurred, this incomplete selectivity could result from a competitive isomerisation of the ion pair formed initially by the *meta* OH group into the isomeric ion pair, involving the *ortho* one. In the event, the use of excess benzyl bromide should speed up the benzylation process, thus improving both the yield and the selectivity. Indeed, stirring **4a** with a fourfold excess of BnBr and Hünig base (1 equiv.) gave pure **4b** in a fairly good yield (71%).

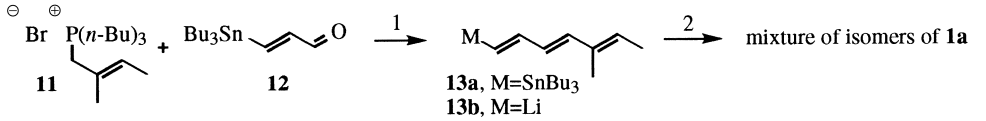
Preparation of the acid **5a** was achieved by first converting the known alcohol **10a**[1] into the sulfone **10d** via, respectively, **10b** and **10c** by sequential treatment with TIPSTf and 2,6-lutidine, MeI and KH, and finally, MCPBA. Monoallylation of **10d** in standard conditions (*n*-BuLi, HPMT, allyl bromide, THF) proceeded quantitatively to afford **5d**, which was desulfonylated by treatment with sodium amalgam to give **5e** (Scheme 3). Finally, oxidation of **5e** by using the $RuCl_3$-$NaIO_4$ reagent furnished **5a**, then esterified (CH_2N_2) to **5b**. Treatment of **5b** by KOH in methanol, followed by evaporation of the solvents to dryness and treatment of the resulting potassium salt by oxalyl chloride in the presence of DMF then furnished the pure acid chloride **5c**.

Condensation of the phenol **4b** with **5c** in a two-phase system proceeded well and the resulting ester **3** (77%), was reacted with NaH in DMSO.[4] The crude product thus obtained was then treated by AcOH and HCl to give **6b**, admixed with its deprotected derivative **6c**. Treatment of this mixture with TBAF finally gave the pure chromone **6c** (81%),[4] eventually transformed into the aldehyde **6a** by oxidation with the Swern reagent. Final conversion of **6a** to the stigmatellin derivative **1c** was briefly examined.



Scheme 3. Reagents and conditions: (1) (i) TIPSTf (1 equiv.), 2,6-lutidine (3 equiv.), CH_2Cl_2, 0°C, 1 h (100%); (ii) KH (1.4 equiv.), ICH_3 (3.8 equiv.), THF (4.5 ml/mmol); –78°C to rt, 2 h (96%); (iii) MCPBA (2.5 equiv.), $NaHCO_3$ (5 equiv.), CH_2Cl_2 (4 ml/mmol); 0°C to rt, 1 h (95%); (2) (i) 1.3 M (in hexane) *n*-BuLi (1.3 equiv.), HMPA (1.3 equiv.), allyl bromide (1.5 equiv.), THF (5 ml/mmol); –78°C, 1 h (100%); (ii) NaHg (1.6 g/mmol, 4 equiv.), $NaHCO_3$ (1 equiv.), MeOH (5 ml/mmol); –20°C to rt, 17 h (88%); (iii) $NaIO_4$ (4.1 equiv.), $RuCl_3{\cdot}xH_2O$ (0.2 equiv.), 1:1 CCl_4:CH_3CN (4.5 ml/mmol); rt, 15 h (67%); (iv) 0.45 M CH_2N_2 in ether (excess); rt, 10 min, then AcOH; (v) 3 M aqueous KOH (1.5 equiv.), MeOH (4 ml/mmol); rt, 15 h, then evaporation to dryness in a vacuum; (vi) $(COCl)_2$ (2 equiv.), DMF (1–3 drops), ether (12 ml/mmol); rt, 3 h, then filtration and evaporation to dryness in a vacuum (76%, from **5e**); (3) 1:1 20% aqueous K_2CO_3/benzene (8 ml/mmol), *n*-Bu_4NHSO_4 (20 mg/mmol), **4b** (1 equiv.); rt, 20 h (77%); (4) (i) see Ref. 4; (ii) $(COCl)_2$ (1.5 equiv.), DIPEA (3 equiv.), DMSO (2.5 equiv.), CH_2Cl_2; –78°C to rt, 0.5 h (74% overall, from **3**)

As indicated (Scheme 4), the phosphonium salt **11** was condensed with the aldehyde **12** in conditions (i.e. in situ generation of the ylide by using *t*-BuOK as a base in THF) known to ensure a high level of *E*-stereoselectivity in relevant Wittig condensations,[5] the crude product being purified by chromatography on Florisil (hexane).



Scheme 4. Reagents and conditions: (1) *t*-BuOK (1.3 equiv.) in THF (1.3 ml/mmol) added to a solution of the salt **11** (1.1 equiv.) and the aldehyde **12** in toluene (2 ml/mmol); 0°C, 0.5 h, then purification on Florisil (41%); (2) 2 M (in hexane) *n*-BuLi (1 equiv.), THF; –85°C, 2 h, then **6a** (1 equiv.), ICH_3 (1.4 equiv.), HMPA (2 equiv.); –85°C to rt, 16 h

The apparently pure (NMR) *all-trans* derivative **13a** thus obtained was then treated by BuLi at low temperature (ca. –85°C) in THF, the resulting mixture being reacted with the aldehyde **6a** and ICH_3 in the presence of HMPT. A complex (TLC, NMR) mixture resulted, but extensive purification by chromatography permitted to isolate in a very low yield (7%) a fraction having R_f (TLC) and spectral (UV, ^{13}C NMR) features similar but *not fully identical* to those of an authentic sample of **1c** prepared from commercial stigmatellin.[6]

In conclusion, notwithstanding the above discrepancies, which could result either from a surprisingly exclusive formation of the unwanted epimer at C-6′ of **1c** in the **13b**–**6a** condensation or, more likely, from some isomerisation of the trienyl residue of **13a** during the Sn–Li exchange (or ensuing steps), the present strategy, which is based on the generation of the chromone residue of **1a** at a later stage of the synthesis, seems promising, permitting generation of an advanced fragment of stigmatellin (i.e. **6**). It is also clear that the procedure we used to elaborate **6a** to **1c** should be substituted to a stepwise, fully stereocontrolled, process so as to allow for confirmation

(or revision) of the structure previously assigned to natural stigmatellin. Results along this line will be published in due course.

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3. (a) Bradley, W.; Robinson, R.; Schwarzenbach, G. *J. Chem. Soc*. **1930**, 793–817; (b) Syper, L. *Synthesis* **1989**, 167–172.
4. Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076–1078. *Protocol for the **3**–**6c** conversion*: To a suspension of NaH (91 mg, 2.27 mmol) in DMSO (12 ml) was added the ester **3** (560 mg, 0.85 mmol), diluted with DMSO (5 ml). After 3 hours stirring at rt, the reaction mixture was slowly poured into a well-stirred, cooled (0°C), saturated solution of oxalic acid in water (30 ml). The resulting mixture was extracted with AcOEt (4×20 ml) and the pooled organic extracts were washed with water (50 ml), and brine (3×25 ml), then dried ($MgSO_4$). The residue left by evaporation of the solvents was taken up in AcOH (4 ml) and a few drops of conc. HCl were added. After 1.5 hours stirring, the resulting yellow solution was evaporated to dryness (rotoevaporator) and the residue was dissolved in AcOEt (20 ml). This was followed by washing with water (20 ml) and the resulting aqueous layer was back extracted with AcOEt (2×10 ml). The resulting, pooled, organic extracts were dried ($MgSO_4$), and evaporated to give an oil which was treated by TBAF (500 mg) in CH_2Cl_2 (10 ml). After 1 hour, the resulting solution was thoroughly washed with brine (5×10 ml), and dried ($MgSO_4$). Evaporation of the solvents gave an oil which was chromatographed on 60 silica gel (hexane/AcOEt) to afford the pure compound **6c** as a colourless oil (337 mg, 81%). The corresponding acetate of **4b** gave the chromone **2b** in moderate yield (49%) in these conditions.
5. (a) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc*. **1998**, *120*, 9084–9085; (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Reviews* **1988**, *84*, 863–927.
6. *Selected data*: compound **8a**: m.p. 123°C; compound **8b**: m.p. 68°C; compound **8e**: m.p. 54°C; compound **4a**: m.p. 128°C; compound **4c**: m.p. 132°C; compound **4b**: m.p. 68°C; compound **10b**: $[\alpha]_D$ –47.9 (*c* 2); compound **10c**: $[\alpha]_D$ –22 (*c* 3.5); compound **10d**: $[\alpha]_D$ +4 (*c* 4.6); compound **5e**: $[\alpha]_D$ +8 (*c* 2.8); compound **5c**: $[\alpha]_D$ +2.8 (*c* 4.5); compound **3**: ^{1}H NMR: 0.92 (d, J = 6.8 Hz, 6H), 1.05–1.19 (m, 24H), 1.36–1.49 (m, 1H), 1.64–1.84 (m, 3H), 2.31–2.5 (m, 2H), 2.79 (q, J = 7.3 Hz, 2H), 2.85 (m, 1H), 3.41 (s, 3H), 3.71 (m, 2H), 3.82 (s, 3H), 3.89 (s, 3H), 4.92 (s, 2H), 6.39 (s, 1H), 7.35 (m, 5H); ^{13}C NMR: 8.2, 12.1, 14.9, 16.9, 18.2, 24.5, 34.5, 37.6, 38.8, 56.2, 61.3, 65.2, 75.1, 87.6, 94.5, 117.5, 127.9, 128.1, 128.4, 134.5, 137.7, 142.2, 153.5, 155.1, 171.9, 202.8; compound **6c**: ^{1}H NMR: 0.91 (d, J = 7 Hz, 3H), 1 (d, J = 6.7 Hz, 3H), 1.46–1.65 (m, 1H), 1.65–1.96 (m, 3H), 1.97 (s, 3H), 2.39–2.82 (m, 2H), 2.83 (m, 1H), 3.39 (s, 3H), 3.5–3.71 (m, 2H), 3.92 (s, 6H), 5 (s, 2H), 6.38 (s, 1H), 7.28–7.48 (m, 5H); ^{13}C NMR: 9.6, 15.6, 16.8, 29.1, 30, 35.8, 37, 56.3, 56.5, 61.4, 66.2, 75.7, 91.8, 92.1, 108.1, 117, 128.2, 128.3, 128.4, 137.5, 141.5, 152.1, 156.1, 156.4, 162.3, 177.5. ^{1}H and ^{13}C NMR in $CDCl_3$ at 200 and 50 MHz, respectively. $[\alpha]_D$ values in CH_2Cl_2. All new compounds have given satisfactory elemental (C, H) analyses. The results presented herein are taken in part from the thesis of L. Domon, Strasbourg (1999).