COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Total synthesis of coleophomone D†

K. C. Nicolaou,* Tamsyn Montagnon and Georgios Vassilikogiannakis

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, USA. E-mail: kcn@scripps.edu

Received (in Cambridge, UK) 22nd August 2002, Accepted 10th September 2002
First published as an Advance Article on the web 10th October 2002

A concise total synthesis of coleophomone D that exists as a dynamic mixture of four isomeric compounds, using a strategy based on a benzoyl cyanide coupling reaction to assemble the key tricarbonyl motif, is reported.

A recent report[1] from a group at Shionogi disclosed the structure and biological activity of the latest member, designated as I-A (**1**, Fig. 1), of a novel class of natural products.[2,3] In line with our recently proposed nomenclature for these compounds,[4] we coined the name coleophomone D for this compound.[5] Coleophomone D was isolated from a broth produced by the fungi *Stachybothys parvispora* Hughes-1952 and the reported biological profile of coleophomone D (**1**) was shown to be akin to its siblings[2,3] and includes antifungal activity[1] and inhibition of human heart chymase.[1,6] The reported structure of coleophomone D (**1**), which it was claimed exists in solution as a mixture of rapidly equilibrating isomers ($D_{1–4}$, **1a–d**, Fig. 1 top), posed an interesting biosynthetic conundrum, since, in addition to the notable absence of the strained macrocycle, it exhibits a different regiochemistry to that of the other members of the coleophomone family (**2–4**, Fig. 2) with respect to the substitution pattern on the aromatic nucleus. In this communication, we wish to report an expedient total synthesis of coleophomone D (**1**)[7] which confirms its existence as a mixture of four isomers, two spirocycles (**1a** and **1c**, diastereoisomers), plus another two isomers which are open-chain keto-aldehydes (**1b** and **1d**, tautomeric atropisomers).

The synthetic challenge posed by coleophomone D (**1**) lies in the construction of the sensitive tricarbonyl moiety with its adjacent quaternary center and 1,2,3-trisubstituted aromatic ring. In aiming for an optimally convergent approach, we chose, in our retrosynthesic analysis, to disconnect coleophomone D (**1**) into two domains (**II** and **III**) through scission of its tricarbonyl moiety in the manner indicated in Fig. 1 (bottom).

Our previous investigations into effecting *C*-acylation of 1,3-diketones, over the preferred *O*-acylation,[4] led us to target the substituted benzoyl cyanide **10** whose construction starting from 1,2-dimethyl anisole (**7**) is shown in Scheme 1. Thus, benzaldehyde derivative **8** was prepared in 83% overall yield from **7** by a modified two-step literature procedure.[8] Treatment of this aldehyde (**8**) with Nagata's reagent afforded the desired cyanohydrin **9** as the major product contaminated with the regio-isomeric acetate formed by migration of the acetyl group (*ca.* 4:1 ratio, 74% combined yield). Oxidation of this mixture with PCC followed by chromatographic separation led to pure benzoyl cyanide **10** in 51% yield.

The synthesis of 1,3-cyclohexenedione **16** proceeded from 5-methyl-1,3-cyclohexadione (**11**) along the pathway shown in Scheme 2. Thus, methylation of **11** followed by sequential prenylations according to our recently developed methodology[4]

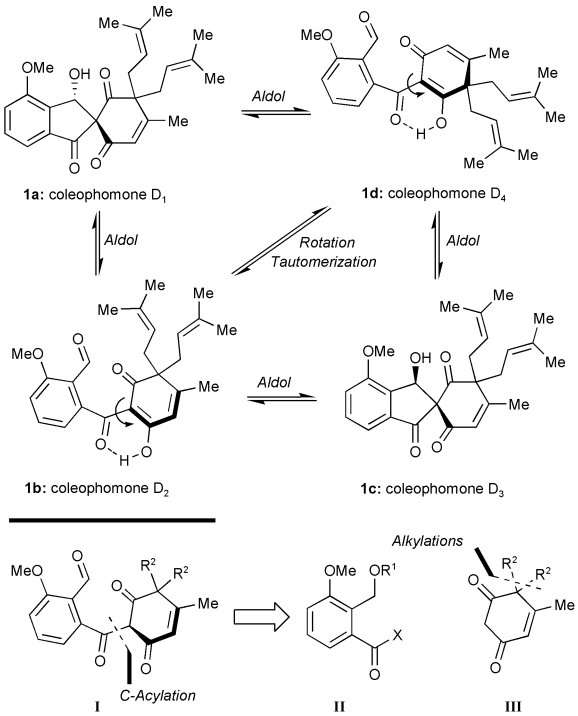


Fig. 1 Isomeric structures of coleophomone D (**1**: D_1–D_4; **1a–d**) (top) and retrosynthetic analysis (bottom).

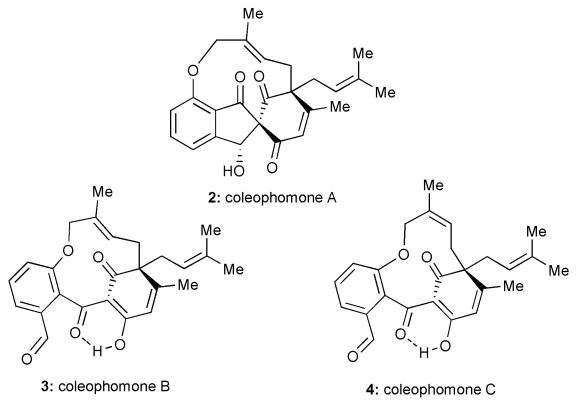
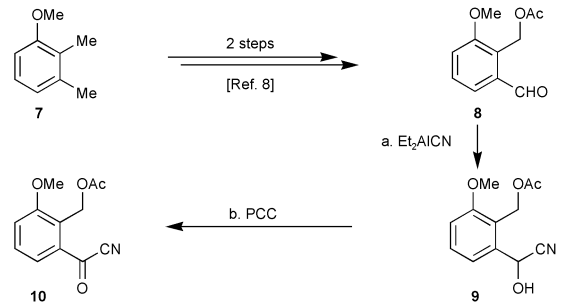


Fig. 2 Stuctures of coleophomones A–C (**2–4**).



Scheme 1 Synthesis of the coupling partner benzoyl cyanide **10**. Reagents and conditions: (a) Et_2AlCN (1.0 equiv), toluene, 0 °C, 2 h, 59% of **9** plus 15% of the regioisomeric migrated acetate; (b) PCC (4.0 equiv), CH_2Cl_2, 40 °C, 4 h, 51%. PCC = pyridinium chlorochromate.

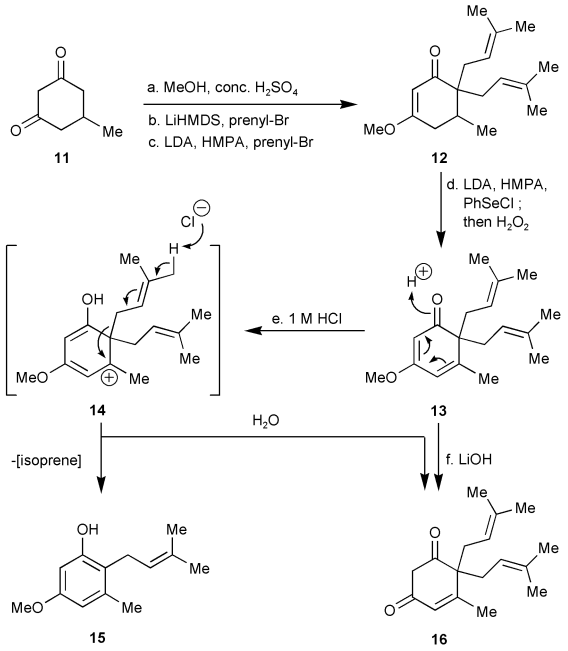
† Electronic supplementary information (ESI) available: selected physical data for compound **18**. See http://www.rsc.org/suppdata/cc/b2/b208236p/

DOI: 10.1039/b208236p

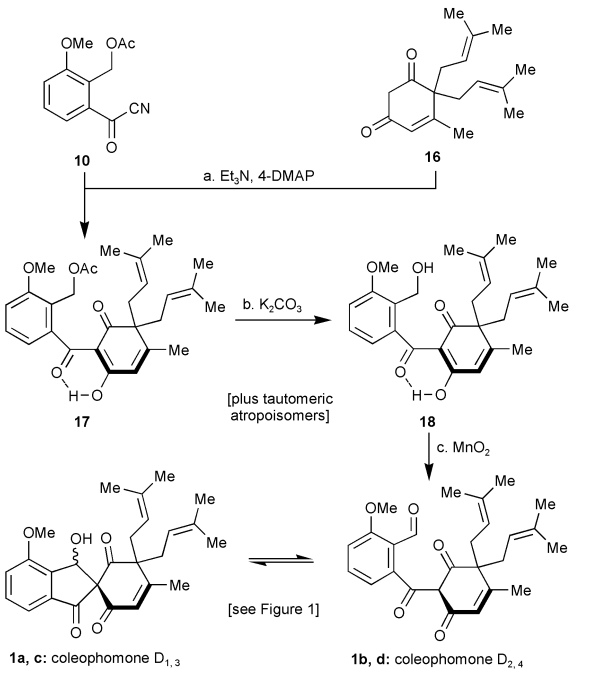
led to compound **12**. Selenation of compound **12** was smoothly accomplished through the formation of its vinylogous enolate (LDA–HMPA, −78 °C) followed by quenching with phenylselenyl chloride (−78 °C) to afford the corresponding phenylselenide which was formed as a mixture of diastereoisomers; the use of HMPA as an additive proved essential for the high yield observed in this transformation. *In situ* oxidation of this selenide with H_2O_2 to the corresponding selenoxides was followed by spontaneous *syn*-elimination forming the desired diene **13** in 78% overall yield. Attempted hydrolysis of the latter compound (**13**) under various conditions using protic acids invariably led to the aromatized product **15** as the major component of a mixture also containing minor amounts of the targeted 1,3-cyclohexenedione system **16**. This rather intriguing transformation (**13**→**15**) presumably proceeds *via* the stabilized carbocation **14** whose conversion to the aromatic system **15** requires loss of a proton and a molecule of isoprene (Scheme 2). In order to circumvent the unanticipated fragility of the intermediates involved in this sequence, hydrolysis of **13** under the alternative basic conditions was explored. Gratifyingly, when this vinylogous ester **13** was treated with LiOH·H_2O in methanol : H_2O (2 : 1) at 80 °C for 12 h, clean conversion to the desired 1,3-cyclohexenedione (**16**) was observed (91% yield).

With requisite building blocks **10** and **16** in hand, the stage was set for their coupling to afford the desired bicyclic systems. To our delight, and contrary to the previous case,[4] the desired coupling reaction to furnish **17** (see Scheme 3) proceeded smoothly and in 80% yield when a full equivalent of Et_3N was added to the reaction mixture without catalytic 4-DMAP in THF at ambient temperature.[4]

Only two steps, acetate cleavage and oxidation, separated coupling product **17** from the targeted molecules. These transformations were readily accomplished by exposure of **17** to K_2CO_3 in methanol to afford alcohol **18** (94% yield) followed by treatment with MnO_2 in refluxing diethyl ether to afford coleophomone D (**1**) (83% yield) as shown in Scheme 3. The ^1H and ^{13}C NMR spectra of synthetic coleophomone D revealed the presence of its postulated isomers (**1a**–**d**) whose signals matched exactly those reported by the Shionogi group.[1]



Scheme 2 Synthesis of the coupling partner 5-methyl-6,6-diprenyl-1,3-cyclohexene-4-dione (**16**). Reagents and conditions: (a) conc. H_2SO_4 (cat.), MeOH, 65 °C, 12 h, 85%; (b) LiHMDS (1.05 equiv), THF, −78 °C, 1 h; then prenyl-Br (1.1 equiv), −78 → 0 °C, 3 h, 85%; (c) LDA (1.1 equiv), THF, slow addition of a solution of the starting material in THF : HMPA = 7 : 1, −78 °C, 1 h; then prenyl-Br (2.0 equiv), −78 → 20 °C, 12 h, 89 %; (d) LDA (2.0 equiv), THF : HMPA = 50 : 1, −78 → 0 °C, 2 h; then PhSeCl (1.5 equiv), −78 → 20 °C, 30 min; then 30% aq. H_2O_2 (excess), 45 °C, 1 h, 78%; (e) 1 M HCl : THF = 1 : 5, 25 °C, 48 h, 50% of **15** plus 30% of **16**; (f) LiOH·H_2O (5.0 equiv), MeOH : H_2O = 2 : 1, 80 °C, 12 h, 91%. LiHMDS = lithium bis(trimethylsilyl)amide; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide.



Scheme 3 Coupling of benzoyl cyanide **10** with dione **16** and completion of the total synthesis of coleophomone D (**1**). Reagents and conditions: (a) **16** (1.0 equiv), **10** (1.0 equiv), Et_3N (2.0 equiv), 4-DMAP (1.0 equiv), THF, 25 °C, 72 h, 80%; (b) K_2CO_3 (3.0 equiv), MeOH, 25 °C, 24 h, 94%; (c) MnO_2 (10 equiv), Et_2O, 36 °C, 4 h, 83%.

In conclusion, an expedient total synthesis of coleophomone D (**1**) based on a convergent strategy comprising of only seven steps from known starting materials (**8**[8] and **12**[4]) has been accomplished. The described synthesis, and that of the related compounds coleophomones B and C,[4] required the development of a benzoyl cyanide-based coupling protocol. Applicable to the selective *C*-acylation of sterically congested 1,3-diketones, this new synthetic technology may find broad applications in organic synthesis and to coleophomone analogue construction. The reported synthesis also serves to confirm the proposed dynamic equilibrium between coleophomones D's four structural isomers (**1a**–**d**) and the different substitution pattern of its aromatic nucleus from that of its more complex relatives coleophomones A–C (**2**–**4**). The latter observation is intriguing in that it may have implications in the biosynthesis of these naturally occurring substances, a puzzling question in itself.

We thank the NIH and the Skaggs Institute for Chemical Biology for financial support.

Notes and references

1 T. Kamigaichi, M. Nakajima and H. Tami, *Jpn. Pat.* 11158109, 1999.
2 T. Kamigaichi, M. Nakajima and H. Tami, *Jpn. Pat.* 10101666, 1998.
3 K. E. Wilson, N. N. Tsou, Z. Guan, C. L. Ruby, F. Pelaez, J. Gorrochategui, F. Vicente and H. R. Onishi, *Tetrahedron Lett.*, 2000, **41**, 8705.
4 K. C. Nicolaou, G. Vassilikogiannakis and T. Montagnon, *Angew. Chem., Int. Ed.*, 2002, **41**, 3276.
5 For nomenclature uniformity, we coined the name coleophomone D for Shionogi's I-A compound,[1] despite the fact that it was not reported by the Merck group in their *coleophoma* sp. study.[3].
6 H. Urata, A. Kinoshita, K. S. Misono, F. M. Bumpus and A. Husain, *J. Biol. Chem.*, 1990, **265**, 22348.
7 An alternate synthesis of coleophomone D was recently presented as a poster at the IUPAC 14th International Conference on Organic Synthesis (ICOS) at Christchurch, New Zealand, July 14–19, 2002 by J. W. Bode, Y. Hachisu and K. Suzuki.
8 V. G. S. Box and G. P. Yiannikouros, *Heterocycles*, 1990, **31**, 1261.