An Attempted Cascade Radical-Mediated Cyclisation Approach to Ring-D Aromatic Steroids

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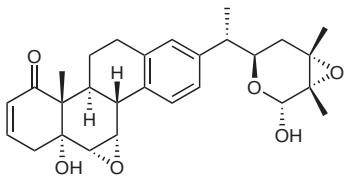
This Letter is dedicated to Richard Heck whose pioneering studies paved the way for the development of a wide range of Pd(0)-mediated coupling reactions in synthesis, especially applications of 'cascades' of Heck reactions in the elaboration of polycyclic constructs including steroids.

Abstract: A synthetic approach to ring-D aromatic steroids, viz. **5**, based on a cascade of radical-mediated cyclisations from the *ortho*-aryl-substituted iododienynones **12** and **13**, instead led to the macrocyclic ketone **16** or to the novel bridged tricycle **17**, respectively, as the major products.

Key words: radical reactions, steroids, polycycles, cascade reactions, nicandrenones

Ring-D aromatic steroids are found only rarely in nature, but some of their number show interesting and unusual biological properties. One such family is the nicandrenones (or 'NICs'), e.g. **1** (Figure 1), isolated from the Peruvian 'shoofly' plant *Nicandra physaloides*, which have insect antifeedant and repellent properties.[1]

Apart from studies by Corey et al.,[2] limited attention has been given to the total synthesis of these compounds, but some detailed studies have been directed toward understanding the origin of ring-D aromatic steroids in vivo.[3]

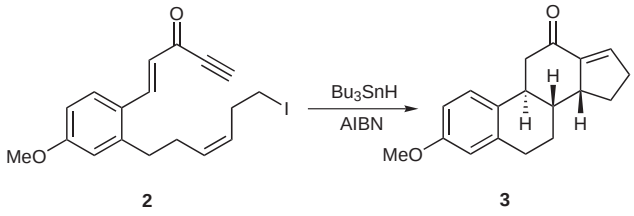


1

Figure 1 Nicandrenone (NIC 1) **1**, insecticidal ring-D aromatic steroid from *Nicandra physaloides*

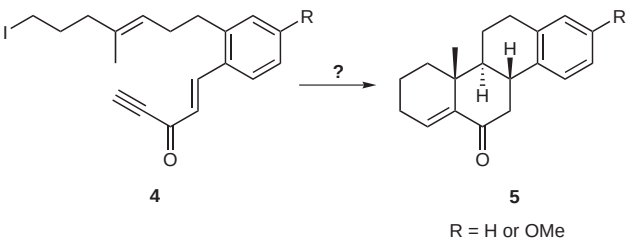
In recent years we have examined a range of complementary radical-mediated cascade cyclisations towards the synthesis of steroids and polycyclic terpenoids.[4] Thus, in one such study we showed that treatment of the iododienynone **2** with Bu_3SnH–AIBN led to the oestrone **3**, via a cascade of 13-*endo*-dig, 5-*exo*-trig and 6-*exo*/*endo* radical cyclisations, in 40% yield (Equation 1).[5]

As part of a proof of principle investigation, we have now examined the corresponding radical chemistry from the structure **4**, related to **2**, as an approach to ring-D aromatic steroids, similar to **1**. The substrate **4** contains a trisubstituted, rather than a disubstituted, double bond and one additional methylene carbon in its top-side chain compared to **2**. By analogy with the conversion **2** → **3**, we anticipated that **4** would undergo a similar cascade of radical cyclisations leading to the tetracycle **5**, a possible progenitor to the nicandrenones (Equation 2).



2 **3**

Equation 1 Cascade radical-mediated cyclisation of the iododienynone **2** to the oestrone **3**



4 **5**

R = H or OMe

Equation 2 Proposed radical-mediated cascade cyclisation towards the ring-D aromatic steroid **5**

We synthesised the *E*- and *Z*-isomers **12** and **13**, respectively, of the iododienynones **4**, in a straightforward manner using identical synthetic sequences, starting from easily available starting materials (Scheme 1).[5,6] Julia olefination reactions[7] between the benzothiazole sulfone **7** and the substituted aldehyde **6**, in the presence of NaHMDS in THF, first led to 2:3 mixtures of *Z*- and *E*-isomers about the newly introduced trisubstituted double bonds of the corresponding alkenes **8a**. Following deprotection to the corresponding alcohols **8b**, the *Z*- and *E*-isomers were separated by routine chromatography. The pure *E*- and *Z*-isomers of **8b** were then converted separately into the *E*- and *Z*-isomeric iododienynones **12** and **13**, respectively, following chlorination to **9a**, reduction and oxidation to **9b**, addition of acetylene, leading to **10**, oxidation to **11** and, finally, chloride–iodide exchange (Scheme 1).

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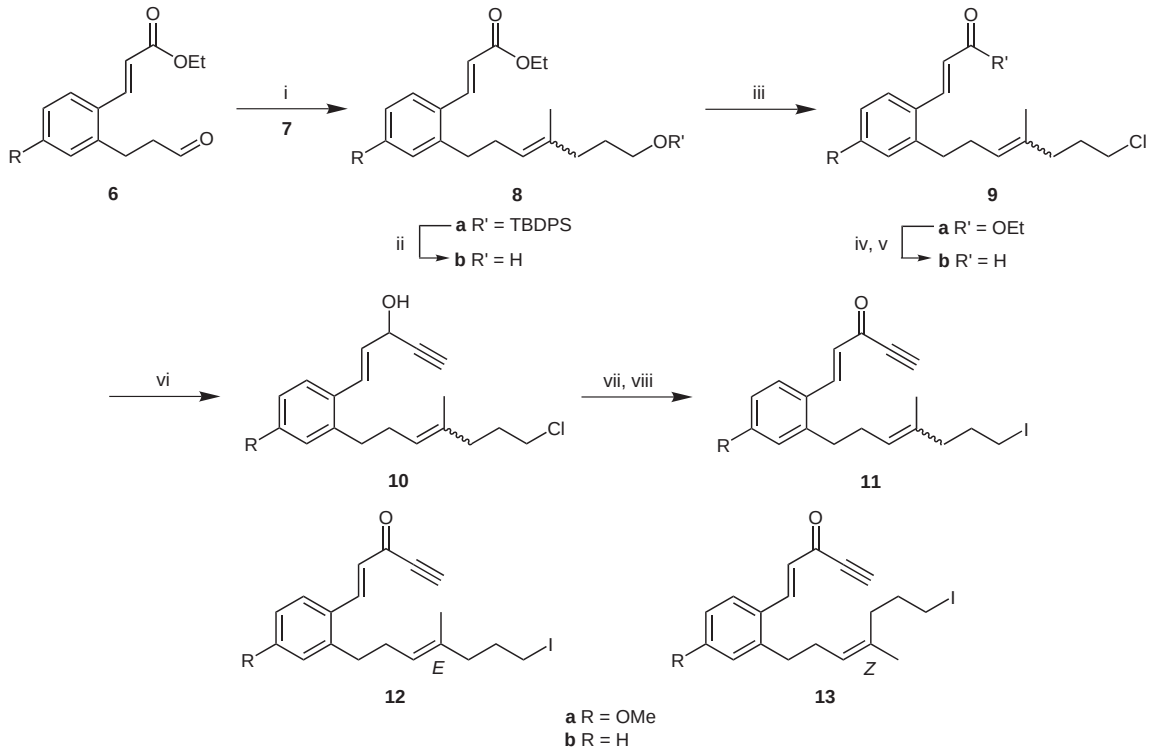


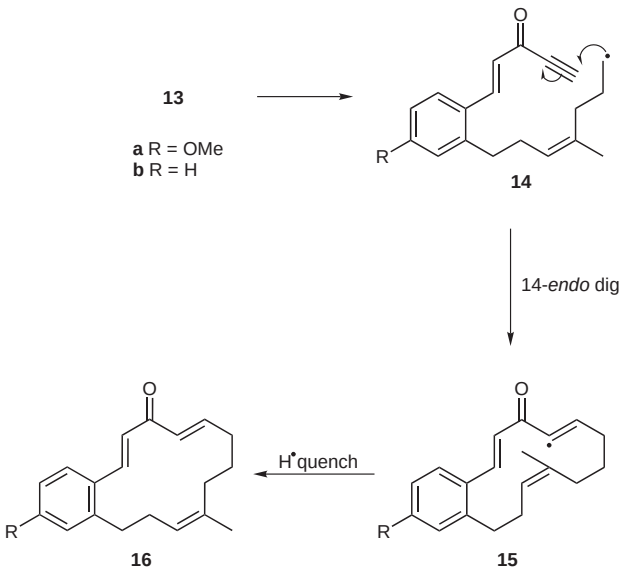
Scheme 1 *Reagents and conditions*: (i) benzothiazole-$SO_2CHMe(CH_2)_3OTBDPS$ (**7**),[6] NaHMDS, THF, –78 °C, 38%; (ii) TBAF, THF, 0 °C → 25 °C, 77%; (iii) NCS, K_2CO_3, PPh_3, CH_2Cl_2, 0 °C, 97%; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 86%; (v) MnO_2, CH_2Cl_2, 89%; (vi) HC≡CMgBr, THF, –78 °C → 25 °C, 98%; (vii) MnO_2, CH_2Cl_2, 86%; (viii) NaI, K_2CO_3, butanone, 92%.

When a solution of the iododienynone **13b** in refluxing benzene was treated with Bu_3SnH in AIBN over 8 hours, work-up and chromatography led to the isolation of a single product in approximately 35% yield. The ^1H NMR spectrum showed that both the *E*-styryl and the *Z*-trisubstituted double bonds in the starting material had been retained in the product, but that the terminal acetylene unit in **13** had been replaced by a new *E*-disubstituted double bond, i.e. δ_H 6.21 (1 H, d, J = 15.0 Hz), 6.58 (1 H, dt, J = 15.0, 7.5 Hz).

Further analysis of the 2D ^1H NMR and ^{13}C NMR spectra supported the macrocyclic structure **16** for the product, resulting from a 14-*endo*-dig cyclisation from the radical intermediate **14** produced from **13**, followed by H-quench at the resulting vinyl radical **15**. A similar product was produced when the substrate **13a** was treated likewise with Bu_3SnH–AIBN under identical conditions (Scheme 2).

The single radical cyclisation of **13** to **16** in comparison with the triple cyclisation of **2** to the oestrone **3** is surprising, bearing in mind that the precursors **2** and **13** differ only by one carbon in the length of their top chains, and that **13** has a trisubstituted rather than a disubstituted double bond in the same carbon chain. Clearly, however, these subtle changes have been sufficient to change the conformational bias of the macrocyclic intermediate **15** to preclude further radical transannular C → C bond-forming reactions at the expense of H abstraction processes. Indeed, the proximity of the vinyl radical centre to the methyl group on the *Z*-trisubstituted double bond in the intermediate **15** could even allow for a facile intramolecular H-radical transfer from this methyl to the vinyl radical via an eight-membered transition state.

If the different outcome seen with the radical cyclisation of **13**, compared with **2**, was not interesting enough, then more was to come when the *E*-isomer corresponding to **13a**, i.e. **12a**, was treated in a similar manner with



Scheme 2 Formation of the macrocycle **16** from the iododienynone **13**.

Bu_3SnH–AIBN in refluxing benzene.[8] This reaction produced a number of products from which an oily mixture of two diastereoisomers of a chemically homogenous polycyclic product was separated by chromatography in approximately 30% yield. Initially, we deluded ourselves into believing that this product was a mixture of diastereoisomers of the hoped for ring-D steroid structure **5** (R = OMe), even though there were some inconsistencies i.e. unaccounted for additional absorptions, in the δ_H = 7.2–7.5 ppm region of the ^1H NMR spectrum. The oily mixture of purified diastereoisomers of the polycyclic phenol methyl ether, resulting from treatment of **12a** with Bu_3SnH–AIBN, was demethylated using BBr_3 leading to a mixture of diastereoisomers of the corresponding polycyclic phenol. The major diastereoisomer was purified by crystallisation and its structure was analysed by X-ray crystallography.

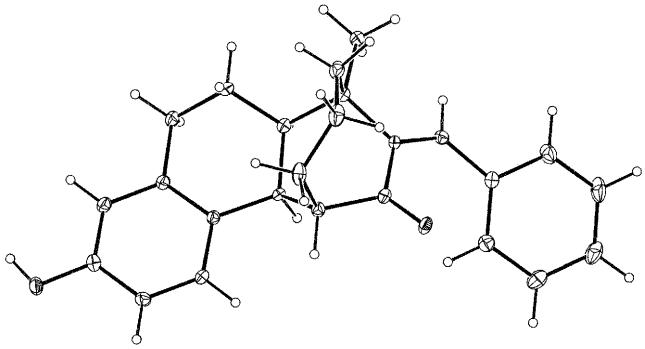
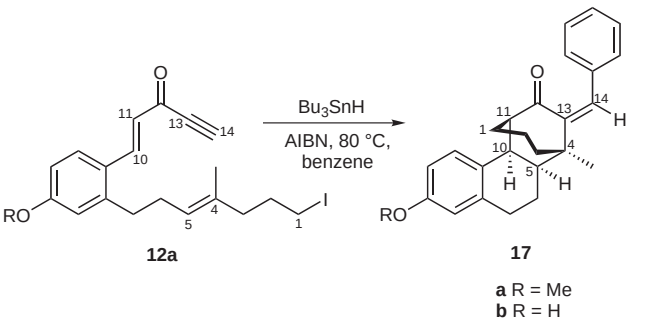


Figure 2 X-ray crystal structure of **17b**

To our amazement the crystal structure analysis (Figure 2)[9] showed that we not only had produced the bridged tricyclic structure **17** rather than the angular 6,6,6-ring system **5**, from the radical cascade but that we had simultaneously incorporated a new benzene ring at the terminus of the ynone electrophore in the original starting material **12a**. This new 'benzene addition' structure (Figure 2) then allowed us to rationalise the inconsistencies we were earlier confused by in the ^1H NMR spectrum of the product (Equation 3).[10]

The formation of the bridged tricycle **17** from the iododienynone **12a** under radical conditions requires three intramolecular carbon-to-carbon bond-forming processes involving C-1 and C-11, C-5 and C-10, and C-4 and C-13, in addition to an intermolecular radical coupling between C-14 and the benzene solvent (see structure **17**). Although the formation of radicals from, and the addition of carbon centred radicals to, benzene and other aryls, is precedented,[11] we have no satisfactory understanding or rational explanation for the formation of the novel bridged tricycle **17** from **12a** under the stated radical conditions. Some radical reactions are known to be promiscuous, and many lead to unusual structures not available by more conventional synthetic methods. The conversion **12a** → **17** is, without doubt, novel and unprecedented, and the unexpected outcome has made us further evaluate our strategy toward ring-D aromatic steroids involving similar radical cascade processes.



Equation 3 Formation of the bridged tricycle **17a** from the iododienyone **12a**

Acknowledgment

We thank the EPSRC and AstraZeneca for their support of this work via a studentship (to DAS).

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(6) The benzothiazole sulfone **7** was prepared from γ-valerolactone in four steps: i) reduction using $LiAlH_4$, ii) protection as the TBDPS ether, iii) coupling to 2-mercaptobenzothiazole, iv) oxidation of the sulphide to the sulphone using MCPBA. See also: Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.

(7) For a review, see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

(8) **Typical Experimental Procedure for the Synthesis of Polycycles 17a and 17b.**
Polycycle 17a.
A solution of tri-*n*-butyltin hydride (170 μL, 0.61 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN; 25 mg, 0.15 mmol) in degassed benzene (20 mL) was added dropwise over 8 h by syringe pump to a stirred solution of the iodide **12a** (200 mg, 0.51 mmol) and AIBN (50 mg, 0.30 mmol) in degassed benzene (200 mL) under reflux and an argon atmosphere. The mixture was heated under reflux for a further 12 h, then

allowed to cool to r.t. and concentrated in vacuo. The residue was purified by column chromatography on silica, using a gradient of 2–10% Et_2O in light PE (bp 40–60 °C) as eluent, to give the bridged tricyclic ketone **17a** (45 mg, 30%) as an inseparable mixture of diastereoisomers in a 2:1 ratio as a colourless oil.

IR (film): 1693, 1612 cm^{-1}. ^1H NMR (400 MHz): δ (major diastereoisomer) = 1.39 (3 H, s, CH_3), 1.47–1.63 (3 H, m), 1.69–1.85 (3 H, m), 2.01–2.19 (3 H, m), 2.67 (1 H, app td, *J* = 15.5, 2.9 Hz, ArCH_aH$_b$), 2.89 (1 H, app dt, *J* = 15.5, 3.4 Hz, ArCH$_a$$H_b$), 3.21 (1 H, ddd, *J* = 8.1, 3.0, 2.4 Hz, C=OC*H*), 3.32 (1 H, dd, *J* = 10.1, 3.0 Hz, ArC*H*), 3.80 (3 H, s, OCH_3), 6.69 (1 H, d, *J* = 2.7 Hz, MeOCC*H*C), 6.77 (1 H, dd, *J* = 8.6, 2.7 Hz, MeOCC*H*CH), 6.87 (1 H, s, PhC*H*), 7.17 (1 H, d, *J* = 8.6 Hz, MeOCCHC*H*), 7.26–7.44 (5 H, m, Ph*H*); δ (minor diastereoisomer) = 1.27 (3 H, s, CH_3), 1.51–1.82 (6 H, m), 1.96–2.19 (3 H,m), 2.81 (1 H, app d, *J* = 8.7 Hz, C=OC*H*), 3.00 (2 H, app t, *J* = 8.4 Hz, ArCH_2), 3.29 (1 H, dd, *J* = 8.7, 1.6 Hz, ArC*H*), 3.79 (3 H, s, OCH_3), 6.68 (1 H, d, *J* = 2.9 Hz, MeOCC*H*C), 6.71 (1 H, s, PhC*H*), 6.78 (1 H, dd, *J* = 8.4 and 2.9 Hz, MeOCC*H*CH), 7.00 (1 H, d, *J* = 8.4 Hz, MeOCCHC*H*), 7.26–7.38 (5 H, m, Ph*H*). ^{13}C NMR (100.6 MHz): δ (major diastereoisomer) = 21.4 (t), 24.7 (t), 24.8 (t), 27.6 (q), 31.2 (t), 36.1 (d), 36.9 (t), 43.4 (s), 45.7 (d), 52.6 (d), 55.2 (q), 112.4 (d), 113.3 (d), 127.8 (2 C d), 127.9 (d), 128.5 (d), 128.7 (s), 129.0 (2 C d), 135.3 (d), 136.9 (s), 140.7 (s), 144.0 (s), 157.4 (s), 205.8 (s); δ (minor diastereoisomer) = 21.8 (t), 23.7 (t), 24.2 (q), 25.9 (t), 29.1 (t), 40.7 (s), 42.9 (d), 46.0 (t), 46.7 (d), 47.3 (d), 55.2 (q), 110.6 (d), 114.4 (d), 124.2 (d), 127.7 (2 C d), 127.8 (d), 129.0 (2 C d), 131.6 (s), 135.0 (d), 136.6 (s), 138.7 (s), 142.6 (s), 158.0 (s), 206.1 (s). ESI-MS: *m*/*z* calcd for: 373.2162; found: 373.2155 [MH^+].

Polycycle 17b.

Boron tribromide (50 μL, 0.53 mmol) was added dropwise to a stirred solution of the tricycle **17a** (50 mg, 0.13 mmol) in anhyd CH_2Cl_2 (10 mL), at –78 °C under a nitrogen atmosphere. The solution was warmed to r.t. slowly over 13 h, and then quenched with H_2O (50 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography, using 10% Et_2O in light PE (bp 40–60 °C) as eluent, to give a 2:1 mixture of diastereoisomers of the phenol **17b** (23 mg, 48%) as a viscous liquid solid. Crystallisation from Et_2O and pentane gave the major diastereoisomer as colourless crystals; mp 195–196 °C. IR (film): 3597, 1693, 1608 cm^{-1}. ^1H NMR (400 MHz): δ (major diastereoisomer) = 1.39 (3 H, s, CH_3), 1.46–1.62 (3 H, m), 1.69–1.85 (3 H, m), 2.01–2.20 (3 H, m), 2.63 (1 H, app td, *J* = 15.6, 3.4 Hz, ArCH_aH$_b$), 2.85 (1 H, app dt, *J* = 15.6, 3.2 Hz, ArCH$_a$$H_b$), 3.19 (1 H, app d, *J* = 10.1 Hz, C=OC*H*), 3.31 (1 H, dd, *J* = 10.1, 3.0 Hz, ArC*H*), 4.71 (1 H, br s, O*H*), 6.62 (1 H, d, *J* = 2.5 Hz, HOCC*H*C), 6.66 (1 H, dd, *J* = 8.3, 2.5 Hz, HOCC*H*CH), 6.89 (1 H, s, PhC*H*), 7.11 (1 H, d, *J* = 8.3 Hz, HOCCHC*H*), 7.27–7.36 (3 H, m, Ph*H*), 7.42 (2 H, app d, *J* = 7.3 Hz, Ph*H*); δ (minor diastereoisomer) = 1.26 (3 H, s, CH_3), 1.47–1.81 (6 H, m), 1.95–2.13 (3 H, m), 2.79 (1 H, app d, *J* = 10.2 Hz, C=OC*H*), 2.93–2.99 (2 H, m, ArCH_2), 3.30 (1 H, dd, *J* = 10.2, 1.9 Hz, ArC*H*), 5.25 (1 H, br s, O*H*), 6.59 (1 H, d, *J* = 2.6 Hz, HOCC*H*C), 6.65 (1 H, dd, *J* = 8.4, 2.6 Hz, HOCC*H*CH), 6.71 (1 H, s, PhC*H*), 6.92 (1 H, d, *J* = 8.4 Hz, HOCCHC*H*), 7.25–7.39 (5 H, m, Ph*H*). ^{13}C NMR (100.6 MHz): δ (major diastereoisomer) = 21.4 (t), 24.7 (t), 24.9 (t), 27.6 (q), 31.0 (t), 36.1 (d), 37.0 (t), 43.5 (s), 45.7 (d), 52.6 (d), 113.7 (d), 114.8 (d), 127.8 (d), 127.9 (d), 128.7 (d), 128.8 (s), 129.0 (d), 135.4 (d), 137.0 (s), 141.0 (s), 144.0 (s), 153.3 (s), 205.9 (s); δ (minor diastereoisomer) = 21.8 (t), 23.8 (t), 24.3 (q), 25.9 (t), 28.9 (t), 40.7 (s), 43.0 (d), 46.0 (t), 46.8 (t), 47.3 (d), 112.3 (d), 115.7 (d), 127.7 (s), 127.8 (d), 128.0 (d), 128.7 (d), 128.9 (d), 135.3 (d), 138.1 (s), 139.3 (s), 144.5 (s), 154.1 (s), 206.7 (s); ESI-MS: *m*/*z* calcd for $C_{25}H_{27}O_2$: 359.2006; found: 359.1999 [MH^+].

(9) **Crystal Data.**
$C_{25}H_{26}O_2$, *M* = 358.46, monoclinic, *a* = 8.7699 (9), *b* = 22.255 (2), *c* = 9.7402 (10) Å, *β* = 95.633 (2)°, *V* = 1891.9 (5) $Å^3$, *T* = 150 (2) K, space group '*Ia*' (No. 9), *Z* = 4, D_{calcd} = 1.259 g cm^{-3}, μ(Mo-K*α*) = 0.078 mm^{-1}, 2181 unique reflections measured and used in all calculations. Final *R*1 [2066 $F > 4\sigma(F)$] = 0.0401 and *wR*2 [all F^2] was 0.0994. Data have been deposited with the Cambridge Crystallographic Data Centre as CCDC 601625; they are available free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(10) An identical 2:1 mixture of diastereoisomers of desmethoxy bridged tricycle, corresponding to **17a**, was obtained (ca. 30%) when the *E*-isomer **12b** was treated similarly with Bu_3SnH–AIBN.

Spectroscopic Data for Desmethoxy 17a.

IR (film): 1694, 1614 cm^{-1}. ^1H NMR (400 MHz): δ (major diastereoisomer) = 1.40 (3 H, s, CH_3), 1.48–1.89 (6 H, m), 1.98–2.24 (3 H, m), 2.68 (1 H, app td, *J* = 15.6, 2.6 Hz, ArCH_aH$_b$), 2.94 (1 H, app dt, *J* = 15.6, 3.5 Hz, ArCH$_a$$H_b$), 3.28 (1 H, app dt, *J* = 8.0, 3.0 Hz, C=OC*H*), 3.38 (1 H, dd, *J* = 10.0, 3.0 Hz, ArC*H*), 6.89 (1 H, s, PhC*H*), 7.08–7.43 (9 H, m, Ar*H*); δ (minor diastereoisomer) = 1.27 (3 H, s, CH_3), 1.48–1.89 (6 H, m), 1.98–2.24 (3 H, m), 2.86 (1 H, app d, *J* = 10.3 Hz, C=OC*H*), 2.99–3.05 (2 H, m, ArCH_2), 3.34 (1 H, app dd, *J* = 10.3, 1.6 Hz, ArC*H*), 6.71 (1 H, s, PhC*H*), 7.08–7.43 (9 H, m, Ar*H*). ^{13}C NMR (100.6 MHz): δ (major diastereoisomer) = 21.4 (t), 24.7 (t), 25.0 (t), 27.6 (q), 30.9 (t), 36.8 (d), 37.1 (t), 43.5 (s), 45.7 (d), 52.4 (d), 55.2 (q), 125.7 (d), 126.4 (d), 127.5 (d), 127.9 (2 C d), 128.0 (d), 129.0 (d), 129.1 (d), 135.4 (d), 136.8 (s), 137.0 (s), 139.6 (s), 144.1 (s), 205.7 (s); δ (minor diastereoisomer) = 21.8 (t), 24.0 (t), 24.3 (q), 25.8 (t), 28.7 (t), 40.7 (s), 43.6 (d), 46.0 (t), 46.5 (d), 47.2 (d), 123.3 (d), 125.4 (d), 126.2 (d), 127.8 (2 C d), 128.6 (2 C d), 128.9 (d), 135.1 (d), 136.6 (s), 137.4 (s), 139.5 (s), 142.6 (s), 206.1 (s). ESI-MS: *m*/*z* calcd for $C_{25}H_{27}O$: 343.2056; found: 343.2053 [MH^+].

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