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Model studies toward the synthesis of the bioactive diterpenoid, harringtonolide

Timothy P. O’Sullivan*a, Hongbin Zhangb and Lewis N. Manderc

In model studies towards the synthesis of harringtonolide, the construction of the tropone moiety via arene cyclopropanation was investigated. The installation of the lactone ring was accomplished by way of a Diels-Alder cycloaddition of various indenones and α-pyrones. The incorporation of the key bridge methyl group and subsequent control of its stereochemistry is also outlined.

Introduction

The diterpenoid tropone, harringtonolide (3), was first isolated in North America from the seeds of Cephalotaxus harringtonia (Taxaceae) and its structure established by X-ray crystallography (Scheme 1).1 It was also isolated in China from C. hainanensis.2,3 and found to have both anti-neoplastic and anti-viral properties, being active against Lewis Lung carcinoma, Walker carcinoma, Sarcoma-180, and L-1210, L-615 and P-388 leukaemias, as well as showing in vitro activity against influenza type A, Newcastle disease, Japanese B encephalitis and vaccinia viruses.4 Harringtonolide is a structurally rigid and congested molecule, consisting of seven adjacent stereocenters. Of particular interest is the presence of the cycloheptatrienone, or tropone, substructure since it is believed that this functionality is responsible for the biological activity of the compound.

While we have previously reported the successful synthesis of harringtonolide by way of an arene-cyclopropanation strategy, the approach had some inherent drawbacks.5-7 In particular, the relatively early formation of the reactive cycloheptatriene moiety and the need to carry out extensive manipulations in its presence had a deleterious impact on yields. It was clear from these difficulties that an improved route to harringtonolide was required. In this new scheme, the cyclopropanation-tautomerisation process would be effected at a much later stage so that fewer subsequent steps would be required. It was proposed that the lactone function be installed by means of a Diels-Alder cycloaddition reaction, while the ether ring would be established using cyclopropyl ring-opening chemistry (Scheme 2). The bulk of the harringtonolide skeleton would thus be in place prior to installation of the cycloheptatriene motif. While the initial [4+2] cycloaddition between the indenone and the pyrone was likely to be problematical, the intramolecular cyclopropanation of the aromatic ring was of greater concern.

This crucial step was not expected to be as favourable as the conversion of 1 to 2 in the previous total synthesis, given the different ring sizes and the potential for competing reactions, such as CH insertion at the benzylic position and/or ylide formation with the lactone carbonyl group.

Scheme 1 Previous synthesis of harringtonolide.

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† Electronic Supplementary Information (ESI) available: [Additional experimental data is available]. See http://dx.doi.org/10.1039/b000000x/
Results and discussion

In order to study this key synthetic step and other aspects of the proposed route to harringtonolide, a series of model studies was initiated. From a geometrical perspective, diazoketone 10 was considered to be a good match for 7 (Figure 1). This was supported by some preliminary computational calculations in which both molecules were overlaid for comparison purposes.

![Figure 1 Molecular geometry comparison.](image)

5-Methoxyindanone (11), prepared in 2 steps from commercially available m-methoxycinnamic acid, was treated with N-bromosuccinimide and triethylamine to afford indenone 12 in 65% yield (Scheme 3). Birch reduction of p-methoxyphenylacetic acid (13) followed by acidification and esterification afforded two isomers 14a and 14b in a 1.5:1 ratio.

As indenone 12 was prone to dimerisation at high temperatures or in the presence of Lewis acids, high pressure activation was instead employed for the [4+2] cycloaddition reaction. When 12 and 14a were subjected to 19 KBar for 24 hours, cycloadduct 15 was obtained as a single product in 52% yield (Scheme 4). The endo stereochemistry was established by NOE differential spectral analysis of the observed correlations between the protons of the ethane bridge with the cyclopentanone ring protons. Methyl ester 15 was hydrolysed to afford acid 16, which was submitted to reduction with lithium triethylborohydride, followed by re-esterification with diazomethane. Following iodoetherification, tetrahydrofuran 19 was obtained in 75% yield over 3 steps from acid 16. The iodide was then subjected to reduction with tri-n-butyltin hydride furnishing methyl ester 20. Hydrolysis of 20 produced carboxylic acid 21 which was subsequently converted to diazoketone 10.
Having secured diazoketone 10, we reached the pivotal step for this initial model study. Based on our previous synthesis, rhodium mandelate was chosen as the catalyst for the initial test. Unfortunately, in our model system, these conditions provided CH-insertion compound 22 as the only isolable product (Scheme 5). A variety of alternative rhodium catalysts, such as Rh$_2$(OAc)$_4$ and Rh$_2$(acam)$_4$, were similarly unsuccessful. Copper(II) acetylacetonate has proven to be an effective catalyst for the cyclopropanation of aromatic rings, but it was unsuccessful in this instance. Finally, the desired product was obtained on treatment of diazoketone 10 with bis(N-t-butylsalicylaldimino) copper(II).

Having demonstrated that geometrical restraints still permitted cyclopropanation to take place, we next turned our attention to the installation of the lactone-ring framework of the harringtonolide molecule by means of a [4+2] cycloaddition reaction with a suitable pyrone (Scheme 6). A high pressure Diels-Alder reaction between 12 and 24 furnished cycloadduct 25 as a single product in 72% yield with the desired endo stereochemistry being confirmed by spectral analysis and X-ray crystallography.

The next phase involved the construction of the internal framework of the molecule. This entailed the formation of an ether bond to introduce the tetrahydrofuran moiety and the incorporation of a bridge methyl group with the correct stereochemistry. Based upon previous work, the prospect of forming the tetrahydrofuran ring in harringtonolide by a process equivalent to 26 $\rightarrow$ 28 appeared to be feasible (Scheme 7).
Accordingly, ketone 25 was reduced to benzylic alcohol 29 in 77% yield (Scheme 8). A combination of diazomethane and a catalytic amount of palladium acetate afforded 30 in almost quantitative yield. Unfortunately, subsequent mercury-mediated ring-opening was wholly unsuccessful, despite recourse to a wide range of reagents and conditions. Attempted iodoetherification of intermediate 29 as per 18 → 19 merely resulted in oxidation of 29 to ketone precursor 25. Additional work would reveal the olefinic bond in 29 to be quite unreactive towards an array of different reagents, most likely a result of the electron-withdrawing nature of the adjacent lactone ring. In an effort to overcome this unexpected lack of reactivity, we decided to incorporate a methyl group into the 4-position of the pyrone, thereby obviating the need for the cyclopropyl ring-opening step entirely and with the additional benefit of increasing the electron density of the olefinic bond of the Diels-Alder adduct. Treating 24 with ethereal diazomethane afforded 32 in 82% yield (Scheme 9). When the newly prepared pyrone 32 and indenone 12 were subjected to high pressure, cycloadduct 33 was obtained. Elaboration of 33 posed an interesting challenge. Attack of an electrophilic reagent on the more exposed face of the olefinic bond would position the methyl group over the aromatic ring with the undesired endo stereochemistry. Accordingly, an indirect strategy was employed. Reduction of 33 to benzylic alcohol 34 followed by hydroboration-oxidation afforded diol 35 with the methyl substituent in the endo location. Oxidation of 35 with the Dess-Martin periodinane furnished diketone 36. Treatment of the diketone with a catalytic amount of DBU effected the epimerisation of 36 to the thermodynamic product 37 with the methyl group now adopting the requisite exo stereochemistry. The transformation of 36 to 37 was manifestly apparent from the 1H-NMR spectrum. The bridge methyl, which had appeared as a doublet at δ0.49 in 36, now had a chemical shift of δ1.35 in 37. This large downfield shift can be ascribed to the removal of the methyl group from the shielding effect of the aromatic ring. Reduction of diketone 37 afforded syn diol 38. Treatment of 38 with para-toluenesulfonic acid led to formation of the benzylic cation and trapping by the remaining hydroxyl to install the tetrahydrofuran ring system (31).

![Scheme 8 Reagents and conditions: i, NaBH₄, rt, MeOH, THF, 77%; ii, CH₂N₂, Pd(OAc)₂, 0°C, Et₂O, 95%.

![Scheme 9 Reagents and conditions: i, CH₂N₂, 0°C, DCM, 82%; ii, CH₂N₂, 0°C, DCM, 82%; iii NaBH₄, rt, MeOH, THF, 85%; iv, BH₃.DMS, 0°C, THF then Et₂NO, reflux, THF, 49%; v, DMP, rt, tBuOH, THF, 48%; vi, DBU, rt, THF, 72%; vii, NaBH₄, rt, MeOH, THF, 66%; viii, p-TsOH, THF, 71%.](attachment:image)
was accompanied by a fragmentation pattern showing loss of nitrogen to produce a peak at m/z 328.

![Scheme 10 Reagents and conditions:](image)

Demethylation of 32 to carboxylic acid 47 by in situ generation of trimethylsilyl iodide proceeded well (Scheme 11). Meanwhile, bromination of indanone 48, a known compound, and subsequent elimination afforded indene 4 in 63% yield. Once again, a high pressure Diels-Alder reaction between 47 and 4 furnished cycloadduct 49 with the required regio- and stereochemistry. 49 was converted to the corresponding acid chloride and then reduced to carbinol 50. This alcohol was subsequently protected as the tert-butylidemethyl silyl ether 51 in good yield.

![Scheme 11 Reagents and conditions:](image)

Applying the previously established methodology, ketone 51 was reduced to the benzylic alcohol 52 and, following hydroboration-oxidation of the olefinic bond, diol 53 was oxidised to diketone 54 (Scheme 12). Treatment of 54 with a catalytic amount of DBU afforded epimer 55 in 98% yield. Interestingly, while the epimerisation of 36 to 37 had provided a 1:3 ratio of endo/exo products, conversion of 54 to 55 went to completion with no starting material remaining. This unexpected result is presumably due to the bulky TBDMs ether side chain, which favours the thermodynamic product through steric interaction. Indeed, MM2 calculations suggest a 2.01 kcal/mol energy difference between 54 and 55 as compared to a gap of only 0.29 kcal/mol between 36 and 37. Reduction of 55, followed by acidic work-up, afforded ether 56 in 64% yield.
Finally, we proposed reducing the lactone to the corresponding lactol, followed by masking of the resultant hydroxyl with a bulky protecting group, namely a TBDMS ether. The reason for the introduction of this group was twofold - first, to block any reaction between the carbenoid and the free hydroxyl and secondly, to direct the carbenoid towards the aromatic ring. Previous studies on gibberellin intermediates had demonstrated that a DIBAL reduction could be conducted in the presence of a dichloroacetate protecting group. With this information in mind, we returned to substrate 56 and the TBDMS ether was cleaved with tetrabutylammonium fluoride to afford the primary alcohol 57, which was then reprotected as the dichloroacetate 58 (Scheme 13). Reduction of 58 with DIBAL at –40°C furnished the desired hemi-acetal 59 in 57% yield. Protection of the hemi-acetal as the TBDMS ether 60 proceeded readily while subsequent hydrolysis of the acetate ester furnished advanced intermediate 61.

Scheme 12 Reagents and conditions: i NaBH₄, rt, MeOH, THF, 89%; ii, BH₃.DMS, 0°C, THF then Et₃NO, reflux, THF, 38%; iii, DMP, rt, tBuOH, THF, 58%; iv, DBU, rt, THF, 98%; v, NaBH₄, rt, MeOH, THF then HCl work-up, 64%.

Scheme 13 Reagents and conditions: i, TBAF, rt, THF, 95%; ii, dichloroacetyl chloride, pyridine, rt, DCM, 96%; iii, DIBAL-H, -40°C, toluene, 57%; iv, TBDMSOTf, N,N-diisopropylethylamine, rt, DCM, 72%; Et₃N, rt, H₂O, MeOH, 90%.

Conclusions

These preliminary model studies have allowed us to investigate the feasibility of a more concise route to the complex diterpenoid, harringtonolide. While our initial studies demonstrated that the geometry of the molecule is suitable for arene-cyclopropanation purpose, we have also uncovered a number of unforeseen obstacles. In particular, the low reactivity of the olefinic bond of the Diels-Alder cycloadduct and the propensity of the \( \alpha \)-diazoketone intermediate to undergo unwanted ylide formation with the lactone ring moiety were problematical. We have successfully incorporated the bridge methyl substituent via the pyrone starting material and have controlled its stereochemical orientation in subsequent work.

Scheme 14 Remaining steps in the synthesis of harringtonolide

Finally, we have modified the chemistry of the lactone ring and incorporated a bulky protecting group in the expectation
of blocking ylide formation and directing cyclopropanation towards the aromatic ring. We hope to report on our work on the remaining steps (Scheme 14) and the completion of this synthesis in due course.

Experimental

General Experimental

Starting materials and reagents used in reactions were obtained commercially and were used without purification, unless otherwise indicated. Flash chromatography was conducted with Merck Kieselgel 60 silica gel as the adsorbent. Proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Varian Gemini 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance (13C-NMR) were recorded on Varian Gemini 300 spectrometer at 75.5 MHz. Infrared (IR) spectra (\(\nu\)) were recorded on a Perkin-Elmer hot-stage and are based on indenone (324 mg, 2 mmol) in carbon tetrachloride (50 ml). The resulting suspension was stirred at 85 °C for a further 2 hours. The solvent was removed under reduced pressure and the residue was treated with sodium sulfate. After filtration, the solvent was removed to give a yellow oil (218 mg, 69%) as a yellow oil; \(\delta_H (300MHz, CDCl_3) 7.40 (1H, d, J = 5.8 Hz, H-3), 7.36 (1H, d, J = 7.7 Hz, H-7), 6.59 (1H, d, J = 2.2 Hz, H-4), 6.58 (1H, dd, J = 2.2, J = 7.7 Hz, H-6), 5.87 (1H, d, J = 5.8 Hz, H-2), 3.82 (3H, s, CH_3O); \(\delta_C (75MHz, CDCl_3) 196.88 (C1), 164.37 (C5), 147.52 (C3), 147.10 (C3a), 128.65 (C2), 124.28 (C7), 122.87 (C7a), 110.97 (C6), 110.36 (C4), 55.53 (CH_3O); m/z 160 (M^+), 145 (2), 132 (10), 117 (18), 106 (12), 89 (87), 78 (5), 74 (28), 70 (68), 66 (10), 61 (100). \mu = 0.86\). Liquid ammonia (150 ml) was added to a solution of 2-(4'-methoxybenzene)-ethanoic acid (13) (3.32 g, 20 mmol) in ethanol (10 ml) and THF (20 ml). Sodium (metal, 3.2 g, 140 mmol, 7 eq.) was added in small pieces over a period of approximately 1 hour until the blue colour persisted for 4 minutes. The ammonia was allowed to evaporate overnight. The residue was washed with water (2×40 ml), brine (40 ml) and dried over sodium sulfate. After filtration, the solvent was removed under reduced pressure and the residue was treated with ethereal diazomethane at 0 °C. After removal of the solvent, the residue was purified by flash chromatography on silica gel (Petroleum ether 40-60°C: ethyl acetate = 100:1→20:1→10:1) to afford an inseparable mixture of the methyl esters (14a: \(\delta_H (300MHz, CDCl_3) 5.69 (1H, d, J = 6.0 Hz, H-C=C), 4.85 (1H, d, J = 6.1 Hz, H-C=C-OC), 3.62 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 3.01 (2H, m), 2.72 (2H, m), 2.25 (2H, s, 2x H-2). \(\delta_C (75MHz, CDCl_3) 202.20 (C9), 71.95 (C12), 59.17 (C10), 52.58 (C9a), 51.64 (COO-C_6H_4), 50.84 (CH_2O-C_6H_4), 46.62 (C4a), 40.41 (C4), 40.11 (C12), 31.01 (C10), 28.30 (C11); m/z 342 (M^+), 311 (12), 279 (3), 265 (15), 254 (6), 241 (30), 229 (10), 217 (10), 195 (10), 173 (10), 161 (5), 127 (5), 115 (10), 93 (5), 71 (5). \mu = 0.73). \(\delta_H (300MHz, CDCl_3) 5.50 (1H, m, J = 6.0 Hz, H-11), 5.08 (1H, dd, J = 2.2, J = 7.7 Hz, H-12), 4.68 (1H, d, J = 7.7 Hz, H-12), 4.55 (1H, m, J = 6.0 Hz, H-11), 4.50 (1H, dd, J = 2.1 Hz, H-12B), 3.85 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.55 (1H, d, J = 7.1 Hz, H-11a), 3.52 (3H, s, CH_3O-C_6H_4), 3.00 (1H, d, J = 7.1 Hz, H-11a), 2.95 (1H, d, J = 13.0 Hz, H-12a), 2.78 (1H, d, J = 15.0 Hz, H-12B), 1.99-1.84 (2H, m, H-10a, H-11a), 1.62-1.42 (2H, m, H-10b, H-11b); \(\delta_C (75MHz, CDCl_3) 196.88 (C1), 164.37 (C5), 147.52 (C3), 147.10 (C3a), 128.65 (C2), 124.28 (C7), 122.87 (C7a), 110.97 (C6), 110.36 (C4), 55.53 (CH_3O); m/z 160 (M^+), 145 (2), 132 (10), 117 (18), 106 (12), 89 (87), 78 (5), 74 (28), 70 (68), 66 (10), 61 (100). \mu = 0.86\). Methyl-2-(1'-methoxy cyclohexa-1',3'-diienyl)ethanoate (14a) and Methyl-2-(1'-methoxy cyclohexa-1',4'-diienyl)ethanoate (14b).
The methyl ester 15 (410 mg, 1.2 mmol) and potassium hydroxide (0.1 g, 18 mmol, 15 eq.) were dissolved in ethanol (25 ml) and water (5 ml). The reaction mixture was stirred at room temperature for 2 hours. 1% (100 g) was added, then acidified with 1M HCl (20 ml) and extracted with chloroform (5x25 ml). The combined organic phase was dried over MgSO4 (575 MHz, CDC13) 171.99 (COO), 159.59 (C6), 143.23 (C4b), 137.54 (C8a), 133.53 (C2), 130.67 (C3), 126.57 (C8), 113.51 (C7), 110.57 (C5), 80.34 (C1), 75.70 (C9), 55.10 (CH2O-C6), 54.32 (C9a), 51.02 (COOCH3), 50.94 (C4a), 50.49 (CH2O-C1), 40.38 (C4), 40.02 (C12), 31.25 (C10), 27.97 (C11); m/z 344 (M+, 10%), 327 (6), 312 (24), 297 (6), 252 (7), 239 (15), 225 (8), 202 (14), 182 (84), 167 (32), 149 (90), 121 (100), 102 (28), 91 (23), 77 (14).

H-removal of the solvent, the residue was purified by flash chromatography on silica gel (Petroleum ether 40-60°C: ethyl acetate = 2:3→0:1→DCM:MeOH = 10:1→5:1) to afford the acid 16 (380 mg, 96.14%), after recrystallisation from ethyl acetate, as colourless needles; mp 221-222 °C (from EtOAc).

Found: C,69.43%; H,6.14%. Calc. for C35H3O5: C,69.50%; H,6.14%. υmax/cm−1 3500 (C=O), 3020 (ArH), 2940 (CH), 1730 (C=O), 1610 (C=O), 1490 (CH2O-C6), 1340 (C=O) (ArOCH3), 1210 (ArOCH3), 1090 (C-O), 1030 (ArOCH3). 1H, 26.92%. Calc. for C20H23O5I: C, 51.08%; H, 4.93%; I, 26.92%. Calc. for C35H3O5: C,69.50%; H,6.14%. υmax/cm−1 3500 (C=O), 3020 (ArH), 2940 (CH), 1730 (C=O), 1610 (C=O), 1490 (CH2O-C6), 1340 (C=O) (ArOCH3), 1210 (ArOCH3), 1090 (C-O), 1030 (ArOCH3); δH (270 MHz, CDCl3) 7.48 (1H, d, J= 8.4 Hz, H-9a), 3.73 (3H, s, CH3O-C6), 3.68 (3H, s, COOCH3), 3.44 (1H, d, J = 8.4 Hz, H-4a), 3.42 (3H, s, CH2O-C1), 2.99 (1H, dd, J = 8.4, J = 8.5 Hz, H-9a), 2.92 (1H, d, J = 15.1 Hz, H-12A), 2.84 (1H, d, J = 15.1 Hz, H-12B), 1.85 (1H, m, H-11f), 1.69 (2H, m, H-10x2), 1.40 (1H, m, H-11b); δC (75MHz, CDC13) 171.99 (COO), 159.59 (C6), 143.23 (C4b), 137.54 (C8a), 133.53 (C2), 130.67 (C3), 126.57 (C8), 113.51 (C7), 110.57 (C5), 80.34 (C1), 75.70 (C9), 55.10 (CH2O-C6), 54.32 (C9a), 51.02 (COOCH3), 50.94 (C4a), 50.49 (CH2O-C1), 40.38 (C4), 40.02 (C12), 31.25 (C10), 27.97 (C11); m/z 344 (M+, 10%), 327 (6), 312 (24), 297 (6), 252 (7), 239 (15), 225 (8), 202 (14), 182 (84), 167 (32), 149 (90), 121 (100), 102 (28), 91 (23), 77 (14).

54

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(1RS,4SR,4aRS,9aSR)-4-Carboxymethyl-1,6-dimethoxy-9-oxo-4,4a,9,9a-tetrahydro-1,4-ethano-1H-fluorene (16).

The alcohol 18 (275 mg, 0.8 mmol) and N-iodosuccinimide (225 mg, 1 mmol) were dissolved in THF (25 ml). The resulting solution was stirred at room temperature under darkness overnight (14 hours), then diluted with ethyl acetate (1 ml) and washed with 5% sodium thiosulfate (Na2S2O3) aqueous solution (2×30 ml) and brine (30 ml). The aqueous phase was extracted with ethyl acetate (20 ml). The combined organic phase was dried over sodium sulfate. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Petroleum ether 40-60°C: ethyl acetate = 2:1→1:1:1) to afford the product 19 (282 mg, 75.3%) as a colourless oil. Recrystallisation from solution ethyl acetate afforded white crystals; mp 116-117 °C (from EtOAc). Found: C, 51.13%; H, 4.87%; I, 26.92%. Calc. for C35H3O5I: C, 51.08%; H, 4.93%; I, 26.92%. υmax/cm−1 3040 (ArH), 2950 (CH), 1730 (C=O), 1610 (C=O), 1490 (CH2O-C6), 1340 (C=O) (ArOCH3), 1210 (C=O), 328 (M+, 2%), 311 (0.7), 300 (1.2), 269 (5), 255 (4), 240 (35), 168 (100), 134 (7), 123 (65), 109 (18), 91 (12), 77 (9), 63 (6).
minutes. After removal of the solvent, the residue was purified by flash chromatography on silica gel (Petroleum ether 40-60°C: ethyl acetate = 2:1→1:1) to afford the product 20 (183 mg, 94.8%) as a colourless oil. Recrystallisation from ethyl acetate afforded colourless crystals; mp 98-99 °C (from EtOAc); Found: C, 69.37%; H, 6.98%. Calc. for C18H24O4: C, 69.75%; H, 7.02%; v_{\text{max}}/cm^{-1} 3005 (ArH), 2950 (CH), 1730 (C=O), 1260 (ArOH), 1150 (C-O), 1085 (C=O), 1030 (ArOH); δ_{H} (300MHz, CDCl3) 7.29 (1H, d, J = 8.2 Hz, H-8), 6.88 (1H, d, J = 2.2 Hz, H-5), 6.75 (1H, dd, J = 2.2, J = 8.3 Hz, H-7), 5.20 (1H, d, J = 5.0 Hz, H-9), 4.09 (1H, d, J = 7.2 Hz, H-2), 3.73 (3H, s, CH3O-C6), 3.65 (3H, s, CH3O-C7), 3.36 (1H, d, J = 8.8 Hz, H-4a), 3.24 (3H, s, CH3O-C8).

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Minor isomer

δ® (300 MHz, CDCl 3) 7.38 (1H, d, J = 8.3 Hz, H-7), 6.82 (1H, dd, J = 2.3, J = 8.3 Hz, H-8), 6.62 (1H, d, J = 2.3 Hz, H-10), 5.36 (1H, d, J = 5.4 Hz, H-6), 4.13 (1H, dd, J = 1.7, J = 8.5 Hz, H-11α), 3.79 (3H, s, CH3O-C9), 3.32 (3H, s, CH3O-C5), 3.22 (1H, dd, J = 1.8, J = 8.7 Hz, H-8), 3.16 (1H, dd, J = 1.7, J = 5.4, J = 8.7 Hz, H-5α), 2.90-1.50 (9H, m).

(2RS,3RS,3aRS,10aRS,10bRS)-3,7-Dimethoxy-2,4-epoxy-1,2,3,3a,4,5-hexahydro-10H,10bH-3,10a-ethanocyclohept[b]acenaphthylen-9-one (23).

A solution of the diazoketone 10 (21 mg, 0.06 mmol) in toluene (5 ml) was added dropwise to a solution of copper (II) bis(N,t-butylsalicylaldiminato) (3 mg) in toluene (3 ml) at reflux. After the addition, the resulting mixture was stirred at reflux for a further 15 minutes. The reaction mixture was cooled to room temperature and one drop of DBU was added.

After stirring for 30 minutes at 40°C (oil bath), the solvent was removed and the residue was purified by flash chromatography on silica gel (Petroleum ether 40-60°C : Ethanol = 1:1→1:5→0:1) to afford the product 22 (5.8 mg, 30%) as a yellow oil; v max/cm−1 2924 (CH), 1730 (C=O), 1660 (C=O), 1245 (CC=O); δ® (300 MHz, CDCl 3) 5.91 (1H, s, H-8), 5.44 (1H, dd, J = 2.6, J = 5.6 Hz, H-6), 4.89 (1H, d, J = 3.7 Hz, H-4), 4.07 (1H, d, J = 5.0 Hz, H-2α), 3.50 (3H, s, CH3O-C7), 3.30 (3H, s, CH2O-C3), 3.11 (1H, d, J = 10.2 Hz, H-10β), 3.01 (1H, m, H-5α), 2.87 (1H, dd, J = 3.8, J = 9.9 Hz, H-3a), 2.10-1.85 (3H, m), 1.70-1.45 (6H, m); δC (75 MHz, CDCl 3) 197.37 (C9,CO), 155.47 (C7), 148.49 (C4a), 143.76 (C10c), 130.04 (C8a), 120.77 (C8), 94.75 (C6), 84.55 (C4), 83.67 (C3), 78.32 (C2), 55.82 (CH2O-C7), 50.29 (C10b), 49.39 (CH3O-C3), 47.43 (C10a), 45.57 (C3a), 38.69 (C12), 34.16 (C11), 33.99 (C10), 32.00 (C5), 19.18 (C1); m/z 326 (M+, 94%), 325 (100), 310 (7), 295 (8), 281 (14), 265 (20), 249 (44), 237 (20), 224 (65), 211 (24), 178 (10), 167 (7), 158 (23), 139 (9), 128 (11), 115 (18), 91 (5), 71 (10).

Notes and references