Total synthesis of the putative structure of the novel triquinane natural product isocapnellenone

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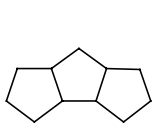
Abstract—A total synthesis of the 'putative structure' **7**, attributed to the novel triquinane sesquiterpene isolated recently from two *Buddelia* species has been accomplished. The spectral data for **7** is a complete mismatch with those reported for the natural product and warrants a revision of the assigned structure.

In recent years, the number of linearly-fused triquinane sesquiterpenoids based on the tricyclo[6.3.0.0^{2,6}]-undecane skeleton **1** has been gradually swelling. These natural products display variation in the disposition of methyl groups and level of functionalization, while embodying the basic framework **1**. Notable examples of different skeletal types among triquinane natural products are coriolin **2** (hirsutane type), cucumin E **3** (isohirsutane type), ceratopicanol **4** (ceratopicane type), pleurotellol **5** (pleurotellane type) and capnellene **6** (capnellane type).[1] Triquinane natural products, many of which exhibit impressive biological activity, have aroused a great deal of synthetic interest during the past two decades.[1,2] In 1995, Romo de Vivar et al. added a new skeletal-type to the triquinane natural products and reported the isolation of isocapnell-9-en-8-one **7** and 6α-hydroxyisocapnell-9-en-8-one **8** from widely occurring plants *Buddleia cordata* and *Buddleia sessiliflora* H. B. K. used in traditional medicine in different regions of the world.[3] Stereostructures of these novel triquinanes **7** and **8** were deduced through extensive ^{1}H and ^{13}C NMR (COSY, HETCOR, COLOC, NOESY) experiments. As **7** and **8** are closely related to capnellanes **6** through the migration of the angular methyl group, the new triquinane skeleton was termed as isocapnellane.[3] It was also surmised that the isocapnellane skeleton need not be derived through methyl migration in an appropriate capnellane precursor but can be formed directly from humulene oxide through the intermediacy of the sesquiterpene africanol.[3]

In view of our long-standing interest[4] in the synthesis of triquinane natural products, isocapnellane structures **7** and **8** attracted our attention. We report here a total



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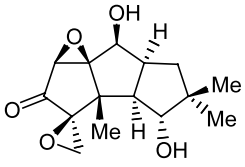

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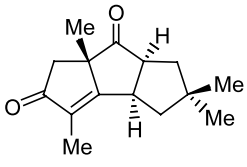

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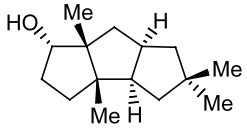

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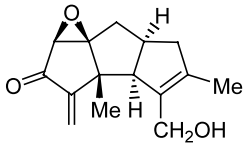

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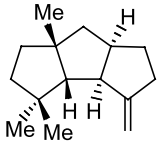

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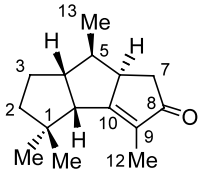
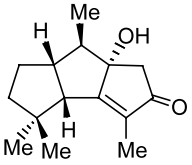


7
"putative structure"



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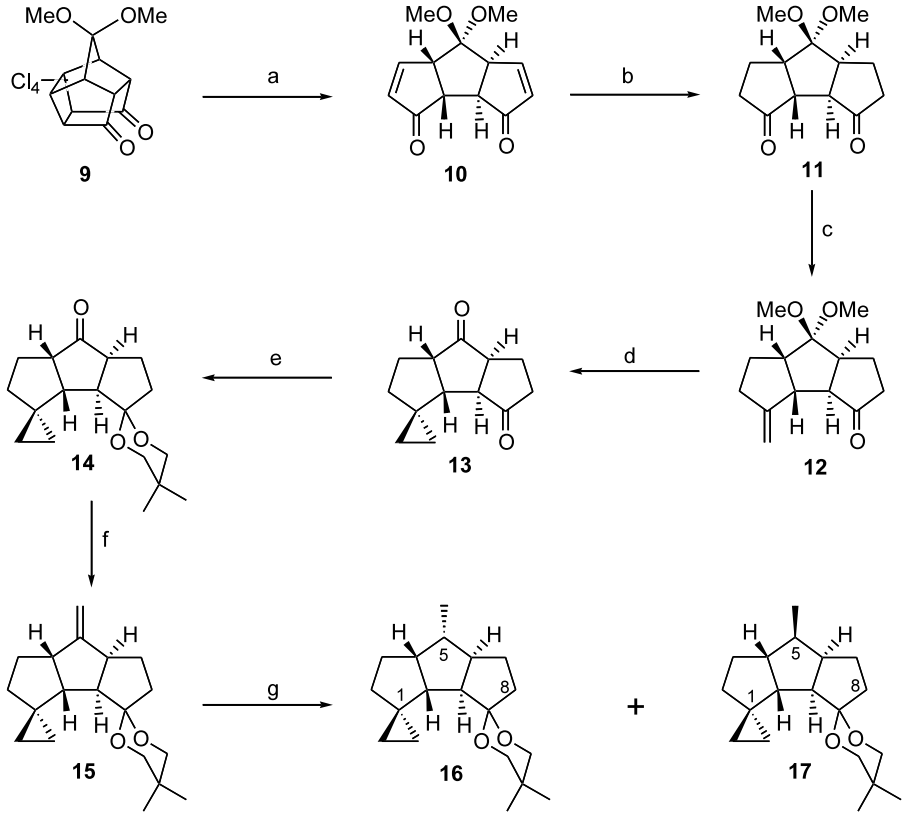
* Corresponding author.

synthesis of tricyclic enone **7**, the structure assigned to the natural product, isocapnell-9-en-8-one, following a variant of the photo-thermal metathesis strategy described by us sometime ago for the synthesis of linear triquinanes.[4a,b] However, we find that the spectral characteristics of the putative structure **7**, synthesized here through an unambiguous route, differ completely from the data reported for the natural product.

Pentacyclic dione **9**,[5] readily available from 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and *p*-benzoquinone in two steps served as the starting point and was elaborated to the *cis*,*anti*,*cis*-fused triquinane bisenone **10** as described recently by us.[4h] Catalytic hydrogenation of **10** to **11** and selective mono-Wittig olefination furnished **12** (Scheme 1).[6] Simmons–Smith cyclopropanation of **12** in the presence of diethylzinc[7] proceeded modestly and resulted in simultaneous deprotection of the dimethylacetal moiety to yield the saturated tricyclic dione **13**. The two carbonyl functionalities in **13** now needed to be differentiated and after some attempts we found that the C9 carbonyl group could be regioselectively protected as the 2,2-dimethyl-1,3-dioxane derivative **14**[6] (Scheme 1).

At this stage, the C5 carbonyl functionality in **14** needed to be transformed into a secondary methyl group with the requisite stereochemistry. Towards this end, **14** was subjected to Wittig olefination to furnish **15**. Catalytic hydrogenation of **15**, as expected, was non-stereoselective and led to a nearly 1:1 mixture of diastereomers **16** and **17** (Scheme 1). While the two diastereomers were readily separable by chromatography, unambiguous assignment of the stereochemistry of



Scheme 1. *Reagents and conditions*: (a) see Ref. 5; (b) H_2, 10% Pd/C,1 atm., EtOAc, rt, 1 h, quant.; (c) $PPh_3{}^+CH_3Br^-$, $^tBuO^-K^+$, benzene, 5°C, 90–95% at 60% conversion; (d) Et_2Zn, CH_2I_2, DCE, 0°C–rt, 18 h, 50–55%; (e) 2,2-dimethylpropanediol, PPTS, benzene, reflux, 8 h, 80–85%; (f) $PPh_3{}^+CH_3Br^-$, $^tBuO^-K^+$, benzene, reflux, 2 h, 85–90%; (g) H_2, 10% Pd/C,1 atm., EtOAc, rt, 1 h, **16**:**17** 1:1, quant.

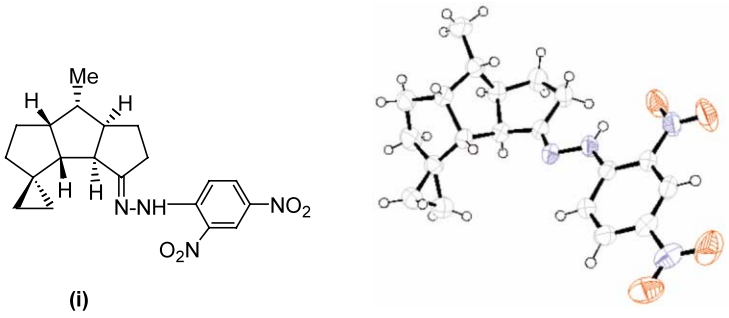
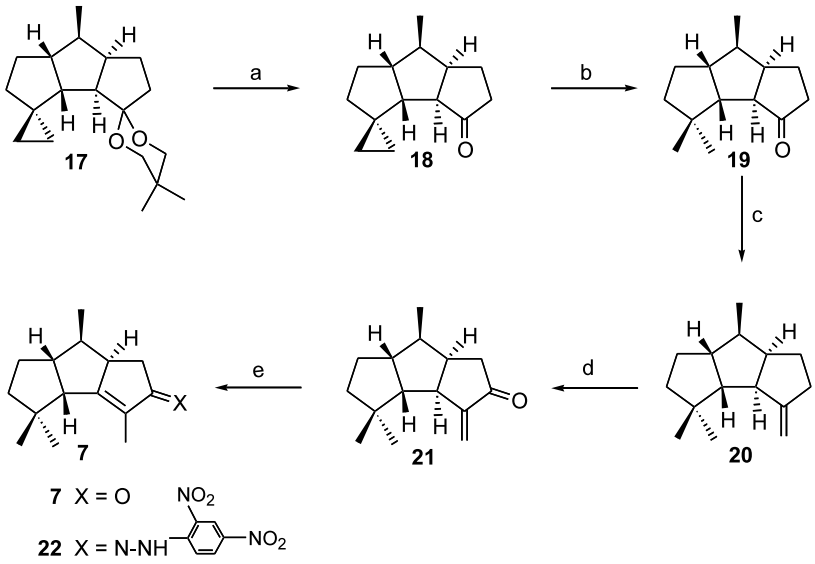


Figure 1.



Scheme 2. *Reagents and conditions*: (a) Amberlyst-15, aq. acetone, 30 min, quant.; (b) PtO_2, H_2, 50 psi, AcOH, 18–24 h, 70% ; (c) $PPh_3{}^+CH_3Br^-$, $^tBuO^-K^+$, benzene, rt, 3 h, 75%; (d) (i) SeO_2, DCM, TBHP, rt, 5 h, 65%, (ii) MnO_2, DCM, rt, 6 h, 75%; (e) PTSA, benzene, reflux, 8 h, 65–70%.

the methyl group at C5 in **16** and **17** from spectroscopic data alone proved difficult and was settled through the X-ray crystal structure determination of a derivative of **16** (Fig. 1).[8]

The diastereomer **17** having the requisite C5 methyl stereochemistry was first taken through the synthesis. Ketal deprotection in **17** led to the ketone **18** and now the *spiro*-fused cyclopropane ring, which had been positioned as a latent *gem*-dimethyl group, was subjected to hydrogenolysis to furnish **19** (Scheme 2).[6] The stage was now set for the generation of the enone moiety and the introduction of the last carbon atom en route to **7**. Wittig olefination in **19** proceeded smoothly to furnish **20**. To introduce the C8 carbonyl functionality, **20** was subjected to catalytic selenium dioxide oxidation to furnish the corresponding allylic alcohol and further oxidized with manganese dioxide to the enone **21** (Scheme 2).[6] On exposure to acid catalysis, the exocyclic double bond in **21** isomerized to the tetrasubstituted position and yielded **7** corresponding to the structure assigned to the natural product.[3] However, the spectral data (UV, IR, ^1H and ^{13}C NMR) for **7** did not match with those reported for the natural product.[3,6] The 2,4-dinitrophenylhydrazone (2,4-DNP) derivative **22** prepared from **7** was also a mismatch with the reported derivative. At this stage, to establish fully the error of the assigned structure of the natural product, we carried out an X-ray crystal structure determination on **22** and the ORTEP diagram is presented in Fig. 2.[9]

Since our synthetic product **7** was not identical with the natural product, our instinctive feeling was to consider the diastereomeric formulation **23** (C5 epimer) as a possible alternative structure for the natural product. With these thoughts in mind, we proceeded to elaborate the C5 epimeric ketal **16** to **23** (Scheme 3). Ketal deprotection in **16** furnished ketone **24** and was subjected to hydrogenolysis to deliver the *gem*-dimethylated product **25** (Scheme 3). Wittig olefination in **25** led to **26** and generated the C_{15}-framework. The carbonyl functionality at C8 in **26** was installed in a two step sequence involving allylic hydroxylation and oxidation to furnish enone **27**. Finally, acid mediated isomerization in **27** led to the targeted structure **23** (Scheme 3). Once again, we found that the spectral characteristics of **23** were completely at variance with those of the natural product but closely resembled that of putative structure **7**.

In summary, we have achieved a total synthesis of the putative structure **7** assigned to the natural product isocapnell-9-en-8-one. We have also outlined a synthesis of **23**, the C5 epimer of **7**. We find that the spectral data for both **7** and **23** are very different from those of the natural product.[3] These observations and a careful scrutiny of the reported spectral data leads to the surmise that the natural products **7** and **8** reported[3] from *B. cordata* and *B. sessiliflora* H. B. K. do not possess a novel triquinane framework and their structure revision is mandated.[10]

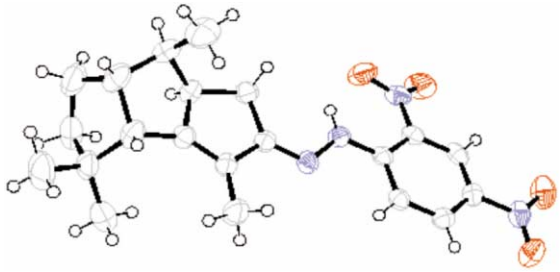
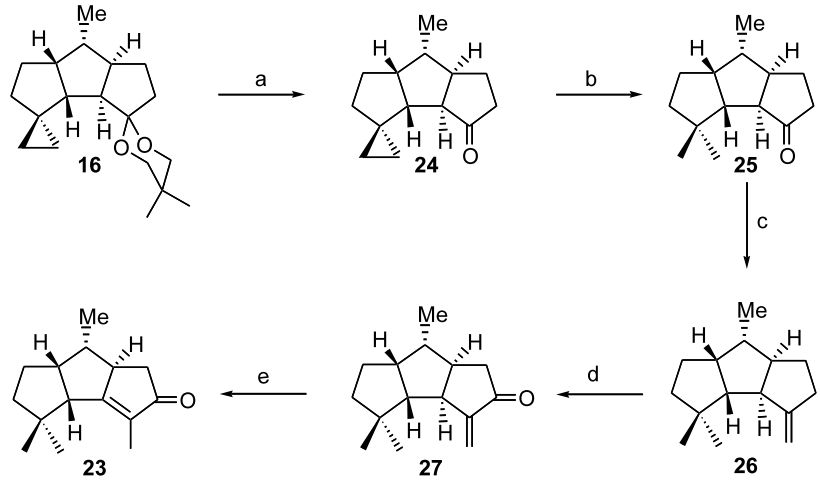


Figure 2.



Scheme 3. *Reagents and conditions*: (a) Amberlyst-15, aq. acetone, 30 min, quant.; (b) PtO_2, H_2, 50 psi, AcOH, 18–24 h, 70% ; (c) $PPh_3{}^+CH_3Br^-$, $^tBuO^-K^+$, benzene, rt, 3 h, 70–75%; (d) (i) SeO_2, DCM, TBHP, rt, 5 h, 60%, (ii) MnO_2, DCM, rt, 6 h, 75–80%; (e) PTSA, benzene, reflux, 8 h, 65–70%.

Acknowledgements

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5. (a) Mehta, G.; Nair, M. S. *J. Am. Chem. Soc*. **1985**, *107*, 7519; (b) Eaton, P. E.; Or, Y. S.; Branca, S. J.; Ravishankar, B. K. *Tetrahedron* **1986**, *42*, 1621; (c) Fessner, W.-D.; Prinzbach, H. *Tetrahedron* **1986**, *42*, 1797.
6. All new compounds reported here were racemic and characterized on the basis of spectroscopic data (IR, ^1H and ^{13}C NMR, mass). Spectral data for some of the key compounds follows. Compound **13**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.99–2.93 (m, 1H), 2.77 (dd as t, $J=8.4$ Hz, 1H), 2.58 (d, $J=9.3$ Hz, 1H), 2.39 (d, $J=8.4$ Hz, 1H), 2.31–1.97 (m, 5H), 1.67–1.59 (m, 1H), 1.37–1.25 (m, 2H), 0.68–0.547 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.45, 220.38, 53.18, 53.07, 50.53, 48.90, 37.22, 35.17, 30.45, 28.90, 23.29, 14.98, 7.83. Compound **15**: ^1H NMR (300 MHz, $CDCl_3$): δ 4.79 (s, 2H), 3.55–3.30 (m, 4H), 3.20–3.05 (m, 2H), 2.28 (d, $J=8.2$ Hz, 2H), 1.99–1.87 (m, 3H), 1.71–1.66 (m, 3H), 1.54–1.45 (m, 1H), 1.28–1.22 (m, 1H), 1.10 (s, 3H), 0.77 (s, 3H), 0.77–0.72 (m, 1H), 0.46–0.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.72, 109.37, 103.83, 72.28, 71.47, 56.95, 50.88, 50.06, 47.82, 35.74, 33.11, 30.05 (2C), 29.51, 28.21, 22.77, 22.16, 14.36, 8.54. Compound **16**: ^1H NMR (300 MHz, $CDCl_3$): δ 3.57–3.51 (m, 2H), 3.48–3.31 (m, 2H), 2.55–2.51 (m, 1H), 2.37–2.32 (m, 1H), 2.14–2.04 (m, 3H), 1.69–1.46 (m, 6H), 1.29–1.25 (m, 1H), 1.13 (s, 3H), 0.93 (d, $J=5.7$ Hz, 3H), 0.82–0.81 (m, 1H), 0.70 (s, 3H), 0.53–0.50 (m, 1H), 0.42–0.36 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.63, 72.33, 71.65, 59.60, 52.75, 52.26, 47.51, 44.07, 36.20, 29.97, 27.91, 27.72, 26.81, 25.74, 22.81, 22.06, 15.63, 15.46, 10.16. Compound **17**: ^1H NMR (300 MHz, $CDCl_3$): δ 3.61–3.28 (m, 4H), 2.55–2.51 (m, 1H), 2.2–2.1 (m, 3H), 2.04–1.87 (m, 1H), 1.78–1.66 (m, 3H), 1.52–1.39 (m, 2H), 1.11 (s, 3H), 1.11–1.05 (m, 1H), 0.93 (d, $J=6.9$ Hz, 3H), 0.91–0.79 (m, 2H), 0.76 (s, 3H), 0.39–0.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.98, 72.54, 71.09, 58.84, 51.16, 50.27, 48.53, 42.70, 35.22, 30.13, 29.95, 29.54, 27.82, 22.65, 22.14, 22.04, 15.02, 14.84, 7.63. Compound **19**: ^1H NMR (300 MHz, $CDCl_3$): δ 2.68–2.58 (m, 1H), 2.44–2.37 (m, 1H), 2.34–2.12 (m, 2H), 2.05–1.99 (m, 1H), 1.90–1.79 (m, 4H), 1.62–1.28 (m, 4H), 1.06 (s, 3H), 0.98 (d, $J=6.9$ Hz, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 221.99, 57.66, 54.76, 50.63, 49.59, 44.92, 41.04, 40.25, 38.98, 29.46, 29.41, 25.23, 21.71, 14.94. Compound **21**: ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (s, 1H), 5.21 (s, 1H), 3.05 (t, $J=7.5$ Hz, 1H), 2.62–2.52 (m, 1H), 2.38–2.23 (m, 2H), 2.13 (d1/2ABq, $J=18.6$, 10.2 Hz,

1H), 1.94–1.78 (m, 3H), 1.53–1.46 (m, 1H), 1.40–1.28 (m, 2H), 1.12 (s, 3H), 0.95 (d, $J=7.5$ Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.02, 151.48, 115.84, 61.59, 51.14, 48.76, 45.75, 44.54, 41.60, 39.89, 38.38, 29.74, 29.31, 25.30, 16.10. Compound **23**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83–2.75 (m, 2H), 2.6 (dd, $J=17.7$, 6.0 Hz, 1H), 2.48–2.43 (m, 1H), 1.91 (dd, $J=17.7$, 2.1 Hz, 1H), 1.79–1.63 (m, 2H), 1.70 (d, $J=2.1$ Hz, 3H), 1.52–1.39 (m, 3H), 1.19 (s, 3H), 1.08 (d, $J=6.6$ Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.75, 184.86, 133.47, 55.52, 51.22, 49.02, 43.89, 42.67, 41.72, 40.53, 30.68, 25.61, 25.53, 14.71, 8.85. Compound **25**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64–2.54 (m, 1H), 2.34–2.12 (m, 5H), 2.06–1.93 (m, 1H), 1.84–1.76 (m, 1H), 1.62–1.46 (m, 3H), 1.43–1.21 (m, 2H), 1.02 (s, 3H), 1.00 (d, $J=6.6$ Hz, 3H), 0.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 224.06, 58.38, 55.53, 49.92, 47.52, 41.81, 41.37, 40.14, 35.07, 29.15, 25.43, 23.24, 21.78, 14.11. Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.05 (d, $J=3.6$ Hz, 1H), 5.24 (d, $J=3.6$ Hz, 1H), 3.00–2.96 (m, 1H), 2.69–2.59 (m, 1H), 2.46 (d1/2ABq, $J=19.2$, 8.1 Hz, 1H), 2.22 (d, $J=19.2$ Hz, 1H), 2.15–2.08 (m, 1H), 1.98 (dd, $J=6.9$, 3.0 Hz, 1H), 1.67–1.46 (m, 3H), 1.42–1.38 (m, 1H), 1.26–1.22 (m, 1H), 1.02 (s, 3H), 0.95 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.01, 150.99, 118.55, 64.47, 49.97, 47.39, 43.69, 43.38, 42.09, 41.14, 39.99, 29.46, 25.55, 23.31, 13.93. Compound **7**: UV (λ_{max}, MeOH): 241 nm; IR (neat): 2955, 2868, 1704, 1662 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (m, 1H), 2.76 (d, $J=7.8$ Hz, 1H), 2.60–2.53 (m, 1H), 2.43 (dd, $J=18.3$, 6.6 Hz, 1H), 2.17–2.14 (m, 1H), 2.08–2.01 (m, 1H), 1.73 (s, 3H), 1.54–1.46 (m, 3H), 1.3–1.22 (m, 1H), 1.14 (s, 3H), 0.97 (s, 3H), 0.61 (d, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.79, 183.86, 134.43, 54.38, 53.35, 46.24, 44.92, 41.93, 39.20, 36.91, 32.36, 30.13, 25.84, 15.12, 9.13.; For comparison purposes, the spectral data reported[3] for the natural product is reproduced here: UV (λ_{max}, MeOH): 260 nm; IR (neat): 1694. 1622 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.96 (m, 1H), 2.5 (dd, $J=18.4$, 6.4 Hz, 1H), 2.07 (br dd, $J=18.4$, 2.3 Hz, 1H), 2.0 (m, 1H), 1.73 (d, $J=1.8$ Hz, 3H), 1.7 (m, 1H), 1.6 (m, 1H), 1.5 (m, 1H), 1.48 (d, $J=8.5$ Hz, 1H), 1.3 (m, 1H), 1.25 (s, 3H), 1.02 (s, 3H), 1.0 (m, 1H), 0.8 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 208.2, 176.3, 140.3, 42.5, 40.2, 32.5, 32.3, 31.7, 29.5, 28.5, 25.9, 21.1, 17.4, 16.5, 8.2.

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8. The carbonyl group in ketal **16** was deprotected and converted into the 2:4-dinitrophenylhydrazone derivative (**i**) for X-ray crystal structure determination. *Crystal data for compound **(i)***: Crystal system: monoclinic, space group: $P2(1)/c$, cell parameters: $a=11.714(3)$, $b=15.022(4)$, $c=10.730$ (3) Å; $\beta=93.844(5)°$; $V=1884.14$ Å^3, $Z=4.0$, $F(000)=816.0$, $\mu=0.10$ mm^{-1}, $D_{calcd}=1.355$ g cm^{-3}, $\lambda=0.7107$ Å. Total number of l.s. parameters = 349, R-factor = 0.0532 for 2887 $F_o>4\sigma(F_o)$ and 0.078 for all 3850 data. GOF (S) = 1.094, restrained GOF = 1.094 for all data. Structure was solved by direct methods (SIR-92). Refinement was by full-matrix least-squares using SHELXL-97. An ORTEP diagram with 50% ellipsoidal probability of compound (**i**) is shown in Fig. 1.
9. *Crystal data for compound **22***: Crystal system: monoclinic, space group: $P2(1)/c$, cell parameters: $a=19.600(5)$, $b=7.028(2)$, $c=14.840(4)$ Å; $\beta=90.897(5)°$; $V=2044.10$ Å^3, $Z=4.0$, $F(000)=848.0$, $\mu=0.09$ mm^{-1}, $D_{calcd}=1.295$ g cm^{-3}, $\lambda=0.7107$ Å. Total number of l.s. parameters = 366, R-factor = 0.0623 for 2521 $F_o>4\sigma(F_o)$ and 0.1174 for all 4169 data. GOF (S) = 1.077, restrained GOF = 1.077 for all data. Structure was solved by direct methods (SIR-92). Refinement was by full-matrix least-squares using SHELXL-97. An ORTEP diagram with 50% ellipsoidal probability of compound **22** is shown in Fig. 2.
10. After the acceptance of this paper we have been informed by Professor Romo de Vivar that the isocapnellane structures **7** and **8** assigned by them to the natural products from two *Buddleia* species were in error and have been shown to be identical with the well-known sesquiterpenoids (+)-cyclocolorenone and 1-hydroxycyclocolorenone, respectively (see corrigendum *Phytochemistry* **1996**, *42*, 1709).