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Total synthesis of the fungal metabolite (±)-acremine G: acceleration of a biomimetic Diels–Alder reaction on silica gel

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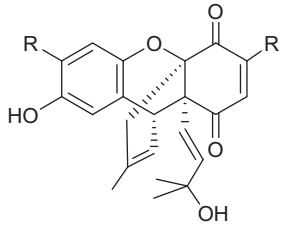
ABSTRACT

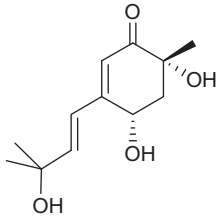
A total synthesis of the bioactive tetracyclic natural product acremine G has been achieved in which a regio- and stereoselective biomimetic Diels–Alder reaction between two readily assembled building blocks, accelerated on a solid support (silica gel), forms the key step.

Endophytic fungi, as they grow on their plant hosts, continually interacting and exchanging evolutionary memories, produce a wide range of novel and interesting secondary metabolites.[1] In particular, fungal metabolites of the genus *Acremonium* have proved to be a rich repository of diverse natural products, endowed with broad-ranging biological activity, encompassing immunosuppressant cyclosporins to tremorgenic indoles.[2] A research group[3] in Italy has explored a strain of *Acremonium byssoides* named A20, isolated from the grapevines of a Sicilian vineyard and found to parasitize *Plasmopara viticola*, for new metabolites. From the cultures of this fungus, a dozen structurally related metabolites named acremines A–F,[3a] G[3b] and H, I, L–N,[3c] originating through a mixed polyketide and mevalonate biosynthetic pathway, were isolated, characterized and their stereostructures elucidated.[3] Among these, acremine G (**1**), whose structure was determined through single crystal X-ray crystallography, is particularly interesting in view of its compact tetracyclic framework and its dimeric relationship with respect to other acremines, for example, acremine A (**2**). As with other acremines, **1** also exhibited mild inhibition of sporangia in *P. viticola*.

In structural terms, acremine G (**1**) possesses an architecture reminiscent of allomicrophyllone **3**, a bioactive



1, R = Me, acremine G
3, R = H, allomicrophyllone



2, acremine A

prenyl benzoquinone dimer from the medicinal plant *Ehretia microphylla*.[4] Drawing on the earlier proposal for the biogenesis of allomicrophyllone **3**, Nasini and co-workers[3b] proposed a Diels–Alder (DA) cycloaddition–enzymatic oxidative coupling-based biosynthetic pathway for acremine G, Scheme 1.[5] The monomeric units **4a** and **5** could readily arise from acremine A (**2**) involving appropriately sequenced dehydration/oxidation steps. Stereoselective Diels–Alder reaction to **6** and further oxidative coupling was expected to lead to **1**. In view of our ongoing interest[6] on acremines that recently culminated in the synthesis of acremines A, B and I,[6] we decided to embark on a synthesis of acremine G (**1**) following the proposed biogenetic pathway involving the Diels–Alder cycloaddition as the pivotal step.[7,8]

To commence our study towards acremine G (**1**) via the biomimetic Diels–Alder cycloaddition strategy, the synthesis of the two monomeric units, diene **4b** and prenylated quinone **5**, was undertaken from readily available starting materials. Methyl hydroquinone **7a**, obtained commercially, was methylated to **7b** and further Vilsmeier–Haack formylation furnished **8**,[9] Scheme 2. Wittig–Horner olefination of **8** led to the cinnamate ester **9**, which, on addition of excess methyllithium, resulted in the tertiary alcohol **10**. After some initial difficulties, we found that **10** could be readily dehydrated with mesyl chloride in the presence of DMAP and Et_3N to deliver the desired diene **4b**,[10] Scheme 2.

The formylated compound **8**[9] also served as the precursor for the prenylated quinone **5**. Demethylation of **8** led to diol **11** and Horner–Wittig olefination furnished the cinnamate ester **12**, Scheme 3. Addition of excess methyllithium to **12** furnished the tertiary alcohol **13**. After investigating several reaction conditions for the oxidation of hydroquinone **13** which would not be detrimental to the sensitive tertiary hydroxy group, we found that aqueous $NaIO_4$ fitted the requirement and delivered the prenylated benzoquinone **5** in good yield.

With somewhat labile diene **4b** and the prenylated benzoquinone **5** in hand, we were keen to avoid thermal activation for the Diels–Alder reaction and looked for mild conditions to affect the cycloaddition. After evaluating several catalysts, we were delighted

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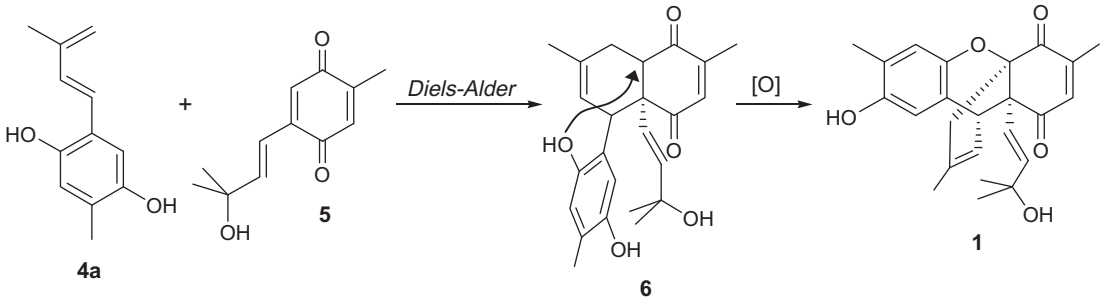
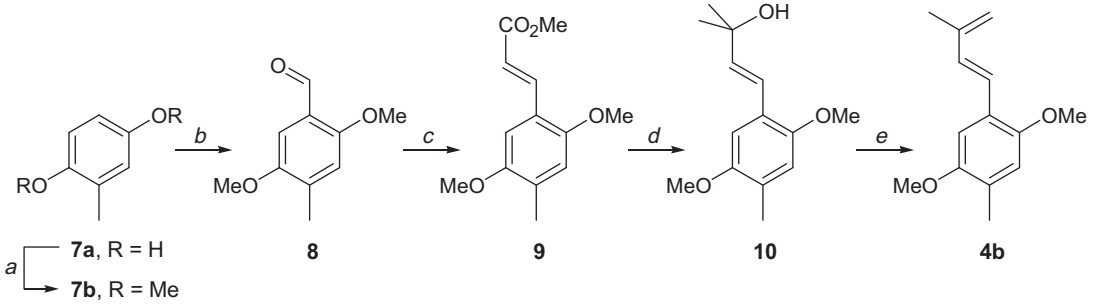


Scheme 1. Proposed biogenesis of acremine G (**1**).

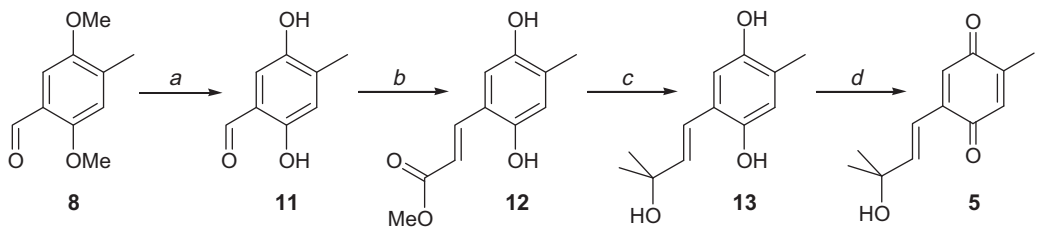


Scheme 2. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, rt, 24 h, quant.; (b) DMF, $POCl_3$, DCE, 80 °C, 12 h, 80%; (c) $Ph_3P{=}CHCO_2Me$, C_6H_6, reflux, 4 h, 80%; (d) MeLi (3 equiv), THF, −78 °C, 30 min, 83%; (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 78%.

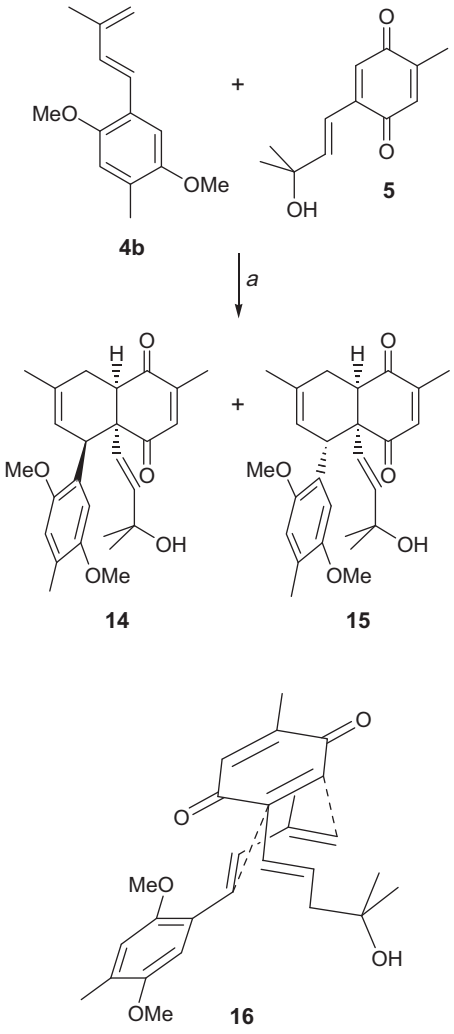
to find that commonly used chromatographic silica gel [100–200 mesh; SiO_2/(**4b**+**5**) = 5:1] accelerated[11] dramatically the DA reaction between **4b** and **5** and the reaction was complete within one hour under ambient conditions to furnish two adducts, *endo*-**14**[10] and *exo*-**15**,[10] in a ratio of 4:1 and in 80% yield, Scheme 4. The structures of **14** and **15** were determined from 2D NMR data, particularly NOE experiments; however, for the sake of unambiguity, the structure of the required *endo*-adduct **14** was fully secured through single crystal X-ray structure determination[12] and its ORTEP diagram is displayed in Figure 1. The stereo- and regiochemical outcomes of the Diels–Alder reaction between **4a** and **5** are quite notable and the preferential formation of the desired *endo*-adduct **14** among other regio- and stereochemical possibilities can be reconciled through the *endo* transition state **16**.[13] Having obtained the key DA adduct corresponding to **6** as envisaged in Scheme 1, the next task was to attempt the crucial oxidative cyclization to the natural product **1** and this a priori necessitated deprotection of the aromatic methyl ether functionality in **14**.[10] However, given the sensitivity of **14**, this proved to be a major hurdle, and forced us to seek a modified approach employing a more pliable protecting group for the phenolic hydroxy groups.

Consequently, the phenolic hydroxy groups in cinnamate ester **12** were protected as the di-TBS derivative **17** and further addition of methyllithium led to the tertiary alcohol **18**, Scheme 5. As expected, the tertiary hydroxy group in **18** proved to be amenable to smooth dehydration and furnished the desired diene **4c** to partner the prenylated benzoquinone **5** in a DA cycloaddition. We were delighted to observe that the DA reaction between **4c** and **5** progressed to completion under ambient conditions[14] in the presence of silica gel [100–200 mesh; SiO_2/(**4c**+**5**) = 5:1] and two adducts, *endo*-**19** and *exo*-**20**, were obtained in ~4:1 ratio, Scheme 6. The structures of **19** and **20** followed from their 2D NMR analyses and spectral comparison with their sibling adducts **14** and **15**, respectively. The preferred formation of the *endo*-adduct **19** was once again along expected lines (vide supra) with good regio- and stereocontrol.

At this stage, we attempted deprotection of the –OTBS groups in **19** to explore the key oxidative coupling (see Scheme 1). However, this deprotection step proved to be surprisingly complicated in spite of employing a variety of desilylation protocols. Thus, we decided to adopt the very recently reported[8] procedure of Stratakis and coworkers to complete the synthesis of acremine G, Scheme 7. Indeed, exposing *endo*-**19** to in situ-generated HF under oxygen and careful monitoring (TLC) of the reaction led to the isolation of acremine G (**1**)[10] in a satisfactory yield through successive desilylation, epimerization and oxidative cyclization. The mechanism of this interesting radical-mediated oxidative coupling reaction has already been dis-



Scheme 3. Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 °C, 24 h, 87%; (b) $Ph_3P{=}CHCO_2Me$, C_6H_6, reflux, 2 h, 88%; (c) MeLi (5 equiv), THF, −78 °C, 1 h, 63% (based on recovered starting material); (d) $NaIO_4$, MeOH/H_2O (2:1), 0 °C to rt, 1 h, 83%.



Scheme 4. Reagents and conditions: (a) silica gel, rt, 1 h, 80% overall (**14** = 64%, **15** = 16%).

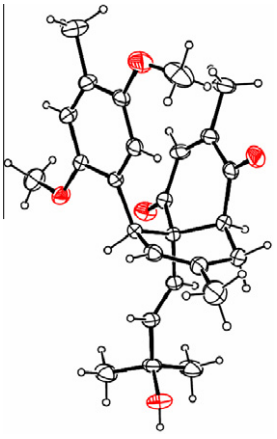
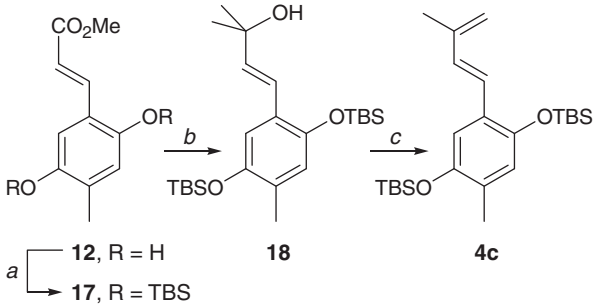
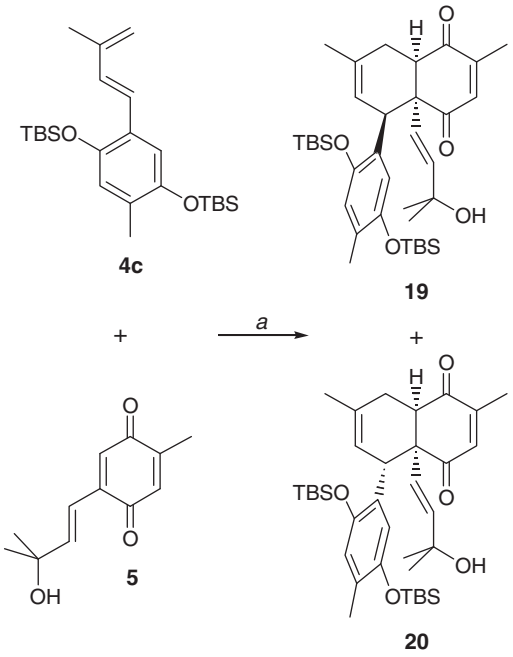


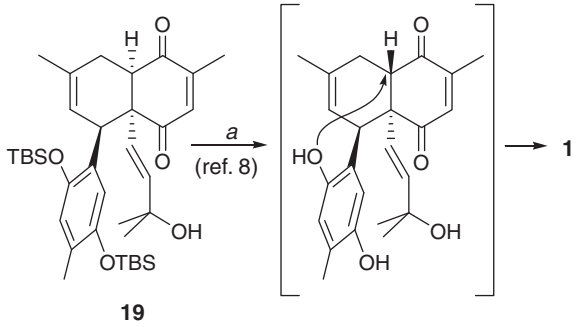
Figure 1. ORTEP diagram of **14**, drawn at 30% probability.



Scheme 5. Reagents and conditions: (a) TBSCl, imidazole, DMAP, DMF, 80 °C, 12 h, 90%; (b) MeLi (3 equiv), THF, −78 °C, 30 min, 88%; (c) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 80%.



Scheme 6. Reagents and conditions: (a) silica gel, rt, 4 h, 77% overall (**19** = 62%, **20** = 15%).



Scheme 7. Reagents and conditions: (a) anhydrous KF, 30% HBr in glacial AcOH, DMF, O_2, rt, 36 h, 70%.

cussed.[8] Our sample of synthetic **1** was found to be spectroscopically (^1H, ^{13}C NMR) identical to the natural product.

In short, we have accomplished a total synthesis of the dimeric natural product (±)-acremine G following a short and simple assembly of the diene and dienophile monomeric units and employing a silica gel-accelerated Diels–Alder reaction as the pivotal step. We are currently extending this successful biomimetic Diels–Alder cycloaddition strategy towards the synthesis of microphyllone, allomicrophyllone and related bioactive natural products.[4]

Acknowledgements

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References and notes

1. For a recent review, see: Guo, B.; Wang, Y.; Sun, X.; Tang, K. *Appl. Biochem. Microbiol.* **2008**, *44*, 136–142.
2. For example, see: (a) Gehrt, A.; Erkel, G.; Anke, T.; Sterner, O. *Nat. Prod. Res.* **2000**, *14*, 281–284; (b) Gatenbay, W. A.; Munday-Finch, S. C.; Wilkins, A. L.; Miles, C. O. *J. Agric. Food Chem.* **1999**, *47*, 1092–1097; (c) Mussaif, M.; Jacques, P.; Schaarwachter, P.; Budzikiewicz, H.; Thonart, P. *Appl. Environ. Microbiol.* **1997**, *63*, 1739–1743.
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6. A manuscript describing the first total syntheses of acremines A, B and I is under the consideration of the Editor for publication in Tetrahedron Letters.
7. While the present research towards acremine G was underway, a biomimetic Diels–Alder-based total synthesis of acremine G appeared in the literature. Although there is convergence in the last step of the synthesis,[8] our approach to acremine G is noteworthy for its brevity and simplicity and the remarkable acceleration of the key Diels–Alder cycloaddition.
8. Arkoudis, E.; Lykakis, I. N.; Gryparis, C.; Stratakis, M. *Org. Lett.* **2009**, *11*, 2988–2991.
9. It was found that methylhydroquinone was not amenable to direct Vilsmeier–Haack formylation and therefore required phenolic group protection.
10. All new compounds reported here are racemic and characterized on the basis of spectroscopic data (IR, ^{1}H, ^{13}C NMR and mass). Spectral data for some of the key compounds are as follows: *compound* **4b**: IR (neat) ν_{max} = 1506, 1463, 1401, 1210, 1045, 971, 872 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.97 (s, 1H), 6.88 (d, J = 16 Hz, 1H), 6.82 (d, J = 16 Hz, 1H), 6.70 (s, 1H), 5.09 (s, 1H), 5.04 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.22 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.88, 150.8, 142.74, 130.97, 127.12, 124.09, 123.36, 116.41, 114.52, 107.89, 56.33, 55.92, 18.70, 16.41 ppm; HRMS (ES) m/z calcd for $C_{14}H_{18}O_2Na$ (M+Na)$^+$: 241.1204; found: 241.1202; *compound* **14**: mp 122–123 °C IR (thin film) ν_{max} = 3436, 2968, 2926, 1675, 1502, 1466, 1210, 1044, 885 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.54 (s, 1H), 6.37 (s, 1H), 5.89 (d, J = 1.5 Hz, 1H), 5.88 (d, J = 16 Hz, 1H), 5.79 (d, J = 16 Hz, 1H), 5.41 (d, J = 3 Hz, 1H), 4.23 (br s, 1H), 3.72 (s, 3H), 3.62 (s, 3H), 2.98 (d, J = 18 Hz, 1H), 2.93 (d, J = 8 Hz, 1H), 2.12 (s, 3H), 1.97 (dd, J = 18, 7 Hz, 1H), 1.83 (s, 3H), 1.52 (d, J = 1.5 Hz, 3H), 1.36 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.62, 198.60, 151.19, 149.90, 147.55, 138.33, 136.14, 133.69, 128.91, 126.64, 126.00, 121.56, 113.79 (2C), 70.85, 57.59, 55.46, 55.32, 48.97, 40.48, 29.86, 29.62, 25.36, 23.40, 16.08, 15.63 ppm; HRMS (ES) m/z calcd for $C_{26}H_{32}O_5Na$ (M+Na)$^+$: 447.2147; found: 447.2145; *compound* **15** mp 142–143 °C IR (thin film) ν_{max} = 3448, 2966, 2926, 1685, 1507, 1466, 1208, 1045, 865 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.62 (s, 1H), 6.52 (s, 1H), 6.49 (d, J = 1.2 Hz, 1H), 5.44 (s, 1H), 5.42 (d, J = 16 Hz, 1H), 5.30 (d, J = 16 Hz, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.35 (t, J = 8 Hz, 1H), 2.33 (br s, 2H), 2.17 (s, 3H), 1.95 (d, J = 1.2 Hz, 3H), 1.75 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.23, 198.96, 151.53, 150.97, 146.27, 139.10, 135.72, 131.17, 127.27, 126.91, 126.10, 123.55, 114.06, 113.27, 70.28, 60.37, 56.69, 56.26, 56.24, 48.41, 29.65, 28.96, 28.83, 23.06, 16.05, 15.87 ppm; HRMS (ES) m/z calcd for $C_{26}H_{32}O_5Na$ (M+Na)$^+$: 447.2147; found: 447.2131; (±)-acremine G (**1**) mp 132–133 °C IR (thin film) ν_{max} = 3370, 2925, 1674, 1420, 1264, 1018, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.51 (s, 2H), 6.36 (q, J = 1.5 Hz, 1H), 5.76 (d, J = 16 Hz, 1H), 5.63 (d, J = 16 Hz, 1H), 5.62 (d, J = 6 Hz, 1H), 5.03 (br s, 1H, OH), 3.75 (d, J = 6 Hz, 1H), 2.72 (d, J = 19 Hz 1H), 2.47 (d, J = 19 Hz, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 1.67 (s, 3H), 1.64 (br s, 1H, OH), 1.21 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.05, 194.09, 150.00, 148.22, 144.35, 142.82, 135.15, 131.29, 124.85, 123.64, 122.51, 121.90, 118.67, 113.57, 80.59, 70.85, 54.85, 38.45, 36.15, 29.60 (2C), 22.6, 16.88, 15.72 ppm; HRMS (ES) m/z calcd for $C_{24}H_{26}O_5Na$ (M+Na)$^+$: 417.1678; found: 417.1621.
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12. Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K using graphite monochromated MoK_α radiation (λ = 0.7107 Å). The X-ray generator was operated at 50 KV and 35 mA. The data were collected with an ω scan width of 0.3°. A total of 606 frames per set were collected using *SMART* in three different settings of φ (0°, 90°, 180° and 270°) keeping the sample at a detector distance of 6.062 cm and the 2θ value fixed at −28°. The data were reduced by *SAINTPLUS*; an empirical absorption correction was applied using the package *SADABS* and *XPREP* was used to determine the space group. The crystal structures were solved by direct methods using *SIR92* and refined by full-matrix least-squares method on F^2 using SHELXL97. CCDC 783610 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. *Crystal data for* **14**: $C_{26}H_{32}O_5$, M = 424.52, triclinic, $P\bar{1}$, a = 15.600(6), b = 18.195(7), c = 20.491(7) Å, α = 115.182(7), β = 104.376(7), γ = 98.049(7)°, V = 4894(3) Å^3, Z = 8, ρ_{calcd} = 1.152 g/cm^3, 39564 reflections measured, 19755 unique (R_{int} = 0.071), R_1 = 0.0858 and wR_2 = 0.1725 for 7188 observed reflections.
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14. Refluxing toluene (110 °C) for 24 h.[8]