Electron-Transfer-Initiated Cascade Cyclizations of Terpenoid Polyalkenes in a Low-Polarity Solvent: One-Step Synthesis of Mono- and Polycylic Terpenoids with Various Functionalities

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A methodology for the one-step synthesis of cyclic polyalkene terpenoids in a low-polarity solvent (dichloromethane) by photoinduced electron transfer (PET) is described. For the efficiency of such processes in low-polarity solvents, the use of the cationic electron acceptor *N*-methylquinolinium hexafluorophosphate is vital. The first direct cyclizations of farnesol and geranylgeraniol to the corresponding all-*trans*-fused 6,6- and 6,6,6-cyclic products are also reported. The mechanism of the termination of the cyclizations is also discussed, isotope-labeling experiments having shown that it proceeds through reduction of the final radical to the corresponding anion, followed by protonation.

Introduction

Photoinduced electron transfer (PET)[1] cyclizations of suitably functionalized acyclic polyalkene terpenoids, which mimic non-oxidative biosynthetic transformations, are shown to be a powerful method for single-step syntheses of mono- and mainly all-*trans*-fused polycyclic compounds.[2−4] Recent investigations along this line revealed that such reactions proceed through radical-type intermediates.[4]

The general methodology in this field, as developed earlier in our laboratory, involves the use of 1,4-dicyanotetramethylbenzene (**4**, DCTMB)[5] and biphenyl (**6**, BP)[6] as an electron acceptor couple in acetonitrile (MeCN), which has been shown to be the best combination for effective product formation (**1a−c** → **2−3** in Scheme 1).[3,4] Reactions are initiated photochemically by the regioselective oxidation of the ω-alkene site of the acyclic starting polyalkene, giving rise to a radical cation. This radical cation formed is trapped in an *anti*-Markovnikov manner by a nucleophile such as water or methanol present in the reaction medium. The resulting neutral radical initiates a cyclization cascade, resulting in a cyclic tertiary radical. Termination of the entire process is achieved either by hydrogen atom transfer to this radical or through the reduction of the final radical center to the parent anion and subsequent protonation.

Our earlier PET methodology involves the use of neutral electron acceptors and donors, with initial formation of radical anion/radical cation pairs upon PET. Normally, efficient product formation is observed only when diffusive separation competes effectively with return electron transfer within the radical ion pairs.[7] For this reason, PET reactions are usually carried out in polar solvents, such as acetonitrile.

The utility of PET cyclization reactions of terpenoid polyalkenes would be greatly increased if low-polarity solvents could be used as reaction media.[7] In this paper we have focused on carrying out PET cyclization reactions of polyalkenes in solvents with lower polarity and coordinating ability than acetonitrile.

Results and Discussion

An electron-transfer-initiated cyclization has recently been used to synthesize cyclic acetals in dichloromethane (DCM).[8] Very high yields were obtained with the use of *N*-methylquinolinium hexafluorophosphate (**5**, NMQ−PF_6)[8,9] as sensitizer and *tert*-butylbenzene as co-sensitizer.

Irradiation of **7a** in a 350-nm Rayonet Photoreactor (RPR-100) in CH_2Cl_2/MeOH (4:1) solution in the presence of DCTMB and BP as electron acceptor couple gave very poor conversions and no product formation even at longer reaction times. When the reaction was conducted under the same conditions but using a cationic electron acceptor, such as NMQ−PF_6 and BP (equimolar) as acceptor couple, the expected product **8** was obtained in 65% yield (Scheme 2).

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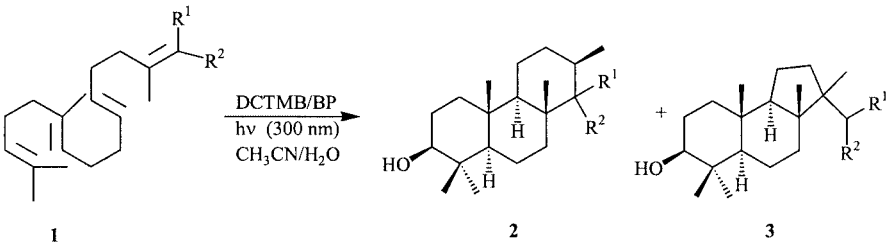
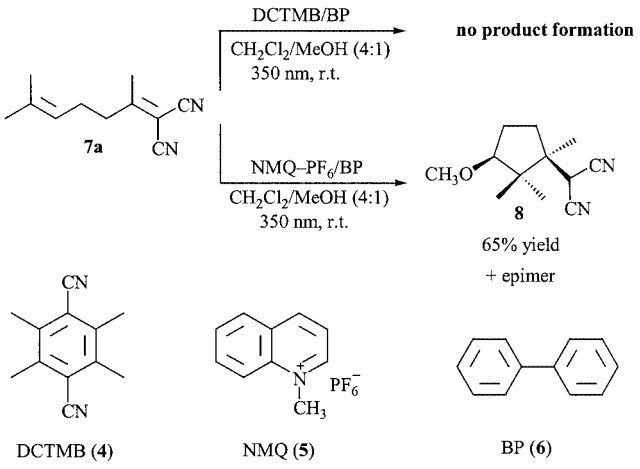
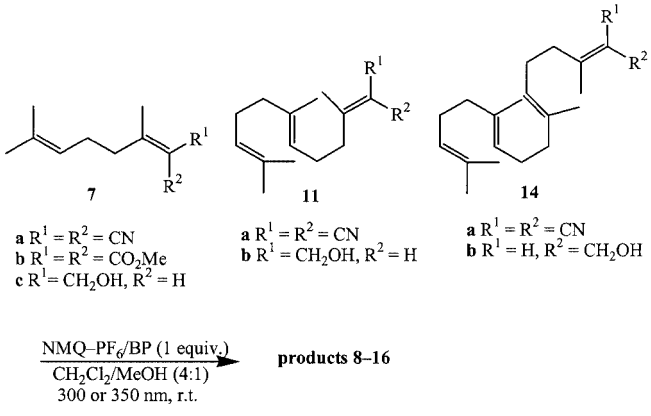


Scheme 1. PET-triggered cyclizations of isoprenoid polyalkenes



Scheme 2. PET cyclization of **7a** under various conditions

In order to explore the utility and scope of this method, a series of substrates with various functionalities were prepared and tested by PET cyclization in DCM with the cationic electron acceptor NMQ−PF_6 together with BP (Scheme 3, Table 1).



Scheme 3. Various substrates for PET cyclizations

The failure of the reaction in DCM with DCTMB and BP as the acceptor couple presumably arises from rapid regeneration of starting materials through back-electron transfer from the DCTMB radical anion to the substrate radical cation. In the case of cation-sensitized reactions on the other hand,[6−9] electron transfer to the excited state of the cationic acceptor from a neutral donor results in the formation of a neutral radical/radical cation pair. Since there is no Coulombic attraction between an anion and a radical, the entire process should be much less dependent on the solvent polarity.

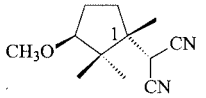
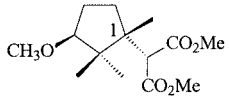
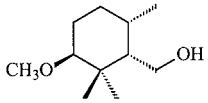
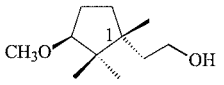
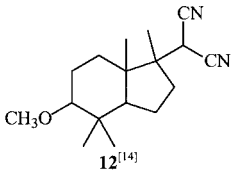
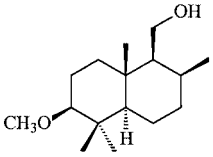
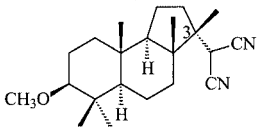
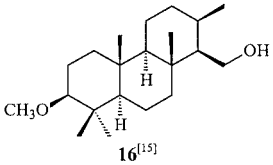
This methodology, which utilizes the "*cationic acceptor principle*", has proven to be effective for the one-step synthesis of both mono- and polycyclic, mainly all-*trans*-fused compounds in a highly selective fashion. With this method a wide variety of substrates can be used as starting polyalkenes, and dinitrile- and diester-substituted polyalkenes in particular give very good yields in the case of monocyclizations and moderate yields in the case of polycyclic products. Here it is worth mentioning that by use of the PET methodology it has been possible, to the best of our knowledge for the first time, to cyclize (*E*,*E*)-3,7-dimethyldodeca-2,6,10-trien-1-ol (farnesol) (Table 1, Entry 5) and (*E*,*E*,*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenol (geranylgeraniol)[10] (Table 1, Entry 7) to afford bi- and tricyclic products, respectively, in a single step by our procedure.

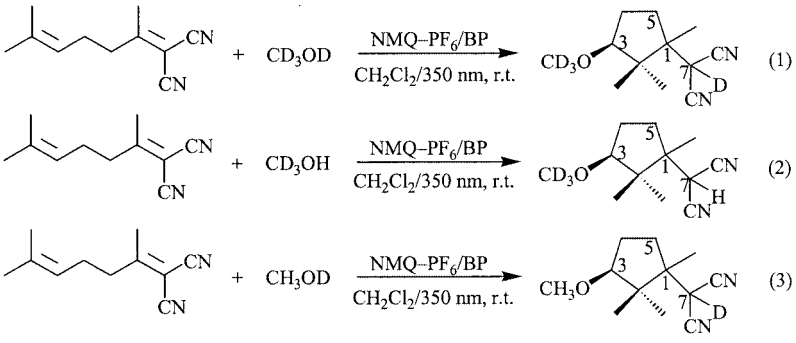
Previous studies[3,16] under polar conditions with DCTMB as electron acceptor suggested that such PET oxidations, generating the parent radical cations, give rise to: (a) trapping of the radical cations by a nucleophile, such as water or methanol in an *anti*-Markovnikov fashion, (b) radical-type cyclization(s), and (c) termination processes, either by reduction and subsequent protonation at the resulting tertiary radical center of the cyclization products or by saturation of this radical center by a hydrogen atom.

On the assumption that the initial reaction steps with NMQ−PF_6/BP-mediated reactions should follow the same route as the reactions with DCTMB/BP in polar solvents, deuterium isotope labeling experiments were carried out [Equations (1)−(3), in Scheme 4] in order to clarify the mechanism of the termination step.

Reactions performed with CH_2Cl_2/CD_3OD solvent mixtures produced a product deuterated at the 7-position [Scheme 4, Equation (1)], indicating methanol as the source of a proton or hydrogen atom.[17] Analogous reactions employing [D_3]methanol (CD_3OH) produced no product deuterated at the 7-position [Scheme 4, Equation (2)], whereas use of a CH_2Cl_2/CH_3OD solvent mixture again produced deuteration at the 7-position [Scheme 4, Equation (3)].

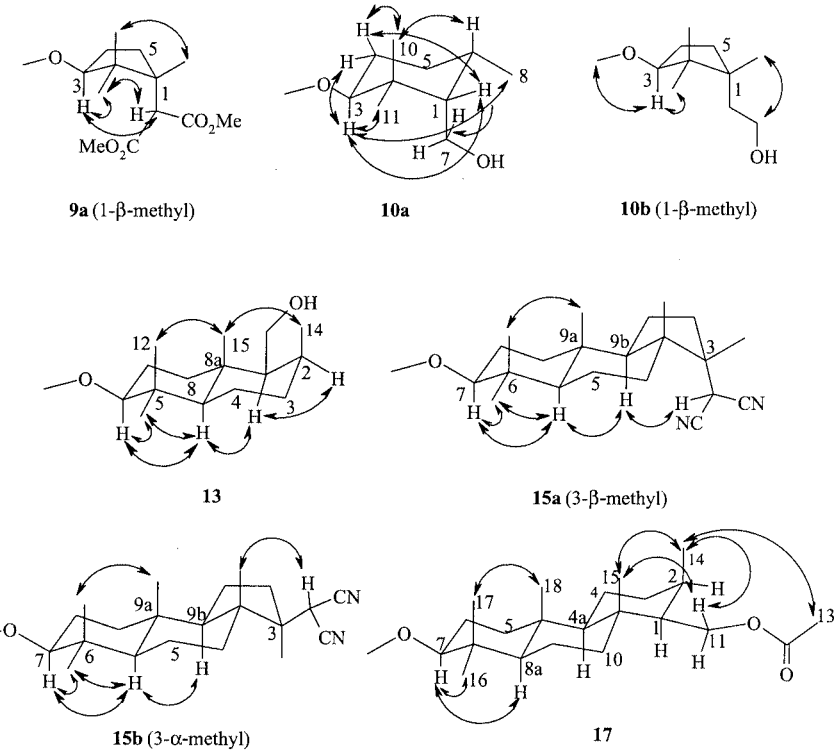
Table 1. Various substrates and corresponding products of PET cyclizations in low-polarity solvents

Entry	Substr.	R^1	R^2	Product[11]	Yield[12] (%)	D.R.[13]
1	**7a**	CN	CN	 **8** + α-methyl isomer at C-1	65	1:1
2	**7b**	CO_2Me	CO_2Me	 **9** + α-methyl isomer at C-1	72	3:1
3	**7c**	CH_2OH	H	 **10a**	11	–
				 **10b** + α-methyl isomer at C-1	8	1.4:1
4	**11a**	CN	CN	 **12**[14]	21	8:3:1
5	**11b**	CH_2OH	H	 **13**	22	–
6	**14a**	CN	CN	 **15** + α-methyl isomer at C-3	28	1:1
7	**14b**	CH_2OH	H	 **16**[15]	9	–



Scheme 4. Isotope labeling experiments

These results strongly suggest that the termination of the cascade cyclization in a low-polarity solvent and with substrates bearing electron-withdrawing groups proceed through reduction of the final radical center to an anion, presumably by the acceptor radical, followed by protonation.



Scheme 5. NOE enhancements and structure identifications

Conclusion

In summary, a combination of the cationic acceptor couple NMQ−PF_6 and BP (as co-acceptor) in the low-polarity dichloromethane/methanol (4:1) solvent mixture can be used to perform efficient cascade cyclizations of terpenoid polyalkenes bearing various functionalities through photochemically initiated electron transfer (PET). The products are mono- and polycyclic terpenoids of synthetic relevance and are accessible in one-step transformations. Notably, under the PET conditions described here, it has for the first time been possible to cyclize (*E*,*E*)-farnesol (**11b**) and all-*trans*-geranylgeraniol (**14b**) to afford bi- and tricyclic terpenoids. Experimental evidence has been found that these reactions, which proceed through *anti*-Markovnikov addition of methanol and subsequent radical cyclization, are terminated by reduction-protonation steps.

These results clearly show that the choice of the electron acceptor(s) and the solvent polarity have a great influence on the reaction outcome and efficiency. A comparative study of different combinations of solvents (i.e., polar vs. low-polarity mixtures) and different acceptor(s) or acceptor couples (neutral vs. cationic) for such PET-triggered cascade cyclizations of terpenoid polyalkenes could be the subject of further studies aiming at improvements.

Experimental Section

Materials and Solvents: Biphenyl (**6**; Fluka; 99%), geraniol (**7c**; Aldrich; 98%), (*E*,*E*)-farnesol (**11b**; Aldrich; 96%), methyl iodide (Fluka; 99%), quinoline (Fluka; 97%), potassium hexafluorophosphate (Aldrich; 99%), and acetyl chloride (Aldrich; 99%) were used as received. Compounds **7a**,[3], **7b**,[18], **14a**,[3] **14b**,[19] and NMQ−PF_6 [20] (**5**) were prepared by literature procedures. Dichloromethane (Merck) was distilled from calcium hydride and stored over molecular sieves (4 Å) in brown bottles under argon. Methanol (Fluka; 99.5%; absolute, over molecular sieves) were used as received without further purification.

Photoreactions: A typical irradiation procedure for reactants is as follows. Cylindrical Pyrex reaction vessels fitted with cooling fingers (water as coolant) and charged with solutions (100 mL, 4:1 DCM/methanol) containing 1 mmol of alkene, 1 equiv. of acceptor (NMQ−PF_6), and 1 equiv. of co-acceptor (BP) were saturated with argon for 30 min and irradiated in a Rayonet RPR-100 photoreactor equipped with 16 lamps (RPR-3500, 8 Watt/lamp). The progress of reaction was monitored by TLC (Merck; silica gel 60 F_{254}), plates being viewed with UV light followed by spraying with acidic vanillin solution (prepared by dissolving 15 g of vanillin in 500 mL of ethanol containing 7.5 mL of concd. H_2SO_4).

Isolation of Products: Reaction products were isolated by column chromatography, performed on silica gel 60 (0.063−0.20 or 0.04−0.063 mm). Products containing diastereomeric mixtures were further separated by HPLC (Merck-Hitachi-L-6000 gradient system coupled with a Knauer differential refractometer and computing system, column; 7-C-18, 250 × 21 mm) except for **8a**−**b**, which were separable by column chromatography.

Characterization of Products: All isolated products were characterized by NMR (^{1}H, ^{13}C, DEPT-90/135, 2D-COSY and HMQC), MS, HRMS, IR and melting point measurements, where applicable. NMR measurements were recorded for $CDCl_3$ solutions with the following instruments: DRX 500 (500 MHz for ^{1}H, 125.8 MHz for ^{13}C), AM 400 (400 MHz for ^{1}H, 100.6 MHz for ^{13}C), ARX 250

(250 MHz for ^{1}H, 62.9 MHz for ^{13}C). Chemical shifts are recorded in δ units (ppm) with the residual $CHCl_3$ resonance assigned at δ = 7.24 ppm in the ^{1}H spectra and the $CDCl_3$ resonance at δ = 77.0 ppm in the ^{13}C spectra. All coupling constants *J* are reported in Hz. High resolution mass spectrometry (HRMS) was performed at 70 eV ionization energy. Infrared spectra (IR) were measured as KBr pellets or liquid films. Melting points were measured with a Reicherd-Wien hot-plate under a microscope and are uncorrected.

Structure Identification: The relative configurations were assigned by NOE and NOESY experiments. NOE abbreviations: s (strong), m (medium) and w (weak); see Scheme 5.

2-(3-Methoxy-1,2,2-trimethylcyclopentyl)malononitrile [8a (1β-methyl)]: This compound was isolated as white solid. M.p. 91−93 °C (ref.[3] 81 °C). IR (KBr): ṽ = 2969, 2246, 1459, 1382, 1119, 1087 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (s, 1 H), 3.35 (dd, *J* = 6.7, 3.8 Hz, 1 H), 3.27 (s, 3 H), 2.08−1.98 (m, 2 H), 1.83−1.75 (m, 1 H), 1.65−1.56 (m, 1 H), 1.29 (s, 3 H), 1.05 (s, 3 H), 0.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.3 (quat), 113.2 (quat), 90.3 (CH), 57.6 (CH_3), 48.3 (quat), 47.9 (quat), 35.1 (CH_2), 31.3 (CH), 26.0 (CH_2), 23.8 (CH_3), 19.8 (CH_3), 18.0 (CH_3) ppm. MS (EI): *m*/*z* (%) = 206 (7) [M^+, $C_{12}H_{18}N_2O$], 141 (6), 109 (22), 100 (7), 83 (61), 71 (100), 55 (19), 41 (15). HRMS (EI): *m*/*z* calcd. for $C_{12}H_{18}N_2O$ 206.1419; found 206.1417.

2-(3-Methoxy-1,2,2-trimethylcyclopentyl)malononitrile [8b (1α-methyl)]: This compound was isolated as white solid. M.p. 62−64 °C (ref.[3] 61 °C). IR (KBr): ṽ = 2997, 2969, 2925, 2819, 2257, 1463, 1383, 1371, 1086 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (s, 1 H), 3.30 (dd, *J* = 6.8, 3.3 Hz, 1 H), 3.26 (s, 3 H), 2.07−1.98 (m, 1 H), 1.92−1.85 (m, 1 H), 1.82−1.77 (m, 1 H), 1.75−1.66 (m, 1 H), 1.40 (s, 3 H), 1.11 (s, 3 H), 0.99 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.9 (quat), 112.4 (quat), 91.9 (CH), 57.6 (CH_3), 48.5 (quat), 47.8 (quat), 36.2 (CH_2), 31.6 (CH), 26.7 (CH_2), 24.8 (CH_3), 20.9 (CH_3), 18.5 (CH_3) ppm. MS (EI): *m*/*z* (%) = 206 (8) [M^+, $C_{12}H_{18}N_2O$], 141 (5), 109 (21), 100 (8), 83 (61), 71 (100), 55 (19), 41 (15). HRMS (EI): *m*/*z* calcd. for $C_{12}H_{18}N_2O$ 206.1419; found 206.1420.

Dimethyl 2-(3-Methoxy-1,2,2-trimethylcyclopentyl)malonate [9a (1β-methyl)]: This compound was isolated as a colorless oil. IR (film): ṽ = 2946, 2879, 1759, 1734, 1457, 1432, 1320, 1239, 1208, 1088 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 3.65 (s, 3 H), 3.46 (s, 1 H), 3.20 (s, 3 H), 3.16 (dd, *J* = 7.5, 3.8 Hz, 1 H), 2.02−1.95 (m, 1 H), 1.82−1.68 (m, 2 H), 1.63−1.56 (m, 1 H), 1.25 (s, 3 H), 0.92 (s, 3 H), 0.85 (s, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 169.1 (quat), 168.9 (quat), 92.2 (CH), 57.4 (CH_3), 57.1 (CH), 52.1 (CH_3), 51.9 (CH_3), 48.5 (quat), 48.1 (quat), 36.3 (CH_2), 27.5 (CH_2), 24.8 (CH_3), 18.5 (CH_3), 18.4 (CH_3) ppm. NOE (saturation−enhancement): δ = 1.25−0.85 (s). 0.92−3.16 (m), 0.85−0.92 (s), 1.25 (s) ppm. MS (EI): *m*/*z* (%) = 272 (2) [M^+, $C_{14}H_{24}O_5$], 241 (7), 199 (50), 140 (100), 125 (31) 109, (20), 85 (24), 71 (24). HRMS (EI): *m*/*z* calcd. for $C_{14}H_{24}O_5$ 272.1624; found 272.1622.

Dimethyl 2-(3-Methoxy-1,2,2-trimethylcyclopentyl)malonate [9b (1α-methyl)]: This compound was isolated as a colorless oil. IR (film): ṽ = 2952, 2879, 1756, 1734, 1434, 1317, 1205, 1102 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.69 (s, 3 H), 3.66 (s, 3 H), 3.48 (t, *J* = 7.7 Hz, 1 H), 3.29 (s, 3 H), 2.10−1.94 (m, 1 H), 1.67−1.56 (m, 2 H), 1.49−1.34 (m, 1 H), 1.20 (s, 3 H), 0.89 (s, 3 H), 0.85 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 168.9 (quat), 168.9 (quat), 88.6 (CH), 58.0 (CH_3), 56.7 (CH), 52.0 (CH_3), 51.9 (CH_3), 47.1 (quat), 44.9 (quat), 35.1 (CH_2), 25.6 (CH_2), 21.3 (CH_3), 18.6 (CH_3), 17.0 (CH_3) ppm. MS (EI): *m*/*z* (%) = 272 (0.2) [M^+, $C_{14}H_{24}O_5$], 199 (57), 140 (100), 125 (29) 109, (40) 100 (12), 71 (25). HRMS (EI): *m*/*z* calcd. for $C_{14}H_{24}O_5$ 272.1624; found 272.1626.

(3-Methoxy-2,2,6-trimethylcyclohexyl)methanol [10a (3β-methoxy)]: This compound was isolated as a yellowish oil. IR (film): ṽ = 3428, 2929, 2868, 1462, 1362, 1082, 1707 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71−3.64 (m, 2 H), 3.33 (s, 3 H), 2.88 (s, 1 H), 2.02−1.96 (m, 1 H), 1.82−1.79 (m, 1 H), 1.63−1.59 (m, 2 H), 1.29−1.21 (m, 1 H), 1.13−1.10 (m, 1 H), 1.05 (s, 3 H), 1.03 (d, *J* = 0.9 Hz, 3 H), 1.01 (dd, *J* = 6.9, 1.2 Hz, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 83.8 (CH), 59.5 (CH_2), 56.8 (CH_3), 49.5 (CH_3), 38.0 (quat), 29.5 (CH), 28.6 (CH_3), 26.7 (CH_2), 25.3 (CH_3), 23.6 (CH_2), 19.5 (CH_3) ppm. NOE (saturation−enhancement): δ = 2.88−3.33 (s), 1.80 (w), 1.61 (w), 1.05 (m), 1.03 (s). 1.99−3.33 (m), 1.60 (m), 1.25 (w), 1.10 (m), 1.03 (ms), 1.01 (s). 1.81−3.33 (m), 2.89 (m), 1.63 (ms), 1.57 (m), 1.27 (w), 1.03 (w). 1.10−3.69 (m), 3.33 (w), 1.99 (w), 1.03 (s). 1.61−3.33 (m), 2.88 (m), 1.24 (s), 1.03 (s). 1.26−3.33 (w), 2.88 (w), 1.99 (w), 1.79 (w), 1.63 (s), 1.01 (w). 1.05−3.69 (m), 3.33 (m), 2.88 (m), 1.99 (w), 1.61 (w). 1.03−3.69 (m), 3.33 (m), 2.88 (s), 2.00 (mw), 1.61 (mw), 1.25 (w), 1.11 (m) ppm. MS (EI): *m*/*z* (%) = 186 (1) [M^+, $C_{11}H_{22}O_2$], 154 (6), 139 (10), 136 (10), 125 (17), 124 (38), 123 (21), 121 (22), 71 (100), 55 (30). HRMS (EI): *m*/*z* calcd. for $C_{11}H_{22}O_2$ 186.1620; found 186.1619.

2-(3-Methoxy-1,2,2-trimethylcyclopentyl)ethanol [10b (1β-methyl)]: This compound was isolated as a colorless oil. IR (film): ṽ = 3410, 2958, 2875, 1779, 1464, 1368, 1110, 1091 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76−3.70 (m, 1 H), 3.68−3.61 (m, 1 H), 3.36 (dd, *J* = 4.2, 8.7 Hz, 1 H), 3.26 (s, 3 H), 2.06−1.95 (m, 1 H), 1.59−1.50 (m, 3 H), 1.48−1.45 (m, 2 H), 0.89 (s, 3 H), 0.85 (s, 3 H), 0.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 90.8 (CH), 60.7 (CH_2), 57.7 (CH), 47.3 (quat), 44.1 (quat), 39.9 (CH_2), 34.3 (CH_2), 27.9 (CH_2), 23.5 (CH_3), 21.1 (CH_3), 17.9 (CH_3) ppm. NOE (saturation−enhancement): δ = 3.73−0.89 (m), 3.64−0.89 (m), 3.36−3.27 (m), 2.00 (m), 0.85 (m) ppm. MS (EI): *m*/*z* (%) = 186 (1) [M^+, $C_{11}H_{22}O_2$], 72 (100). HRMS (EI): *m*/*z* calcd. for $C_{11}H_{22}O_2$ + H 187.1698; found 187.1695.

2-(3-Methoxy-1,2,2-trimethylcyclopentyl)ethanol [10c (1α-methyl)]: This compound was isolated as a colorless oil. IR (film): ṽ = 3405, 2967, 2876, 1744, 1464, 1375, 1111, 1090 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76−3.70 (m, 1 H), 3.68−3.60 (m, 1 H), 3.51 (t, *J* = 7.8 Hz, 1 H), 3.30 (s, 3 H), 2.08−1.98 (m, 1 H), 1.76−1.66 (m, 1 H), 1.60−1.36 (m, 4 H), 0.89 (s, 3 H), 0.85 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 89.2 (CH), 60.3 (CH_2), 58.0 (CH_3), 46.2 (quat), 43.7 (quat), 40.0 (CH_2), 34.6 (CH_2), 26.9 (CH_2), 22.3 (CH_3), 21.8 (CH_3), 17.3 (CH_3) ppm. MS (EI): *m*/*z* (%) = 186 (1) [M^+, $C_{11}H_{22}O_2$], 72 (100). HRMS (EI): *m*/*z* calcd. for $C_{11}H_{22}O_2$ + H 187.1698; found 187.1699.

2-(5-Methoxy-1,4,4,7a-tetramethyl-octahydroinden-1-yl)malononitrile (12a, major isomer): This compound was isolated as a white solid. M.p. 94 °C. IR (KBr): ṽ = 2952, 1473, 1457, 1390, 1139, 1089 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.64 (s, 1 H), 3.24 (s, 3 H), 2.84 (t, *J* = 2.7 Hz, 1 H), 2.25 (m, 1 H), 1.90−1.77 (m, 3 H), 1.74−1.67 (m, 2 H), 1.65−1.54 (m, 3 H), 1.20 (s, 3 H), 1.15 (s, 3 H), 0.99 (s, 3 H), 0.98 (s, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): 113.7 (quat), 113.6 (quat), 84.0 (CH), 57.5 (CH_3), 53.8 (quat), 52.5 (CH), 45.9 (quat), 36.7 (quat), 33.7 (CH_2), 31.2 (CH), 29.6 (CH_3), 26.5 (CH_3), 24.5 (CH_2), 24.1 (CH_2), 21.8 (CH_3), 20.6 (CH_2), 18.5 (CH_3) ppm. MS (EI): *m*/*z* (%) = 274 (4) [M^+, $C_{17}H_{26}N_2O$], 242 (6), 177 (15), 136 (18), 71 (100). HRMS (EI): *m*/*z* calcd. for $C_{17}H_{26}N_2O$ 274.2045; found 274.2047.

2-(5-Methoxy-1,4,4,7a-tetramethyl-octahydroinden-1-yl)malononitrile (12b, next-major isomer): This compound was isolated as a colorless oil. IR (film): $\tilde{\nu}$ = 2926, 2873, 2823, 1468, 1455, 1391, 1366, 1150, 1096, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.72 (s, 1 H), 3.23 (s, 3 H), 2.85 (t, *J* = *2.7* Hz, 1 H), 2.24−2.15 (m, 1 H), 1.88−1.82 (m, 1 H), 1.79−1.75 (m, 1 H), 1.74−1.66 (m, 2 H), 1.64−1.48 (m, 4 H), 1.29 (s, 3 H), 1.22 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 113.0 (quat), 112.5 (quat), 84.0 (CH), 57.6 (CH_3), 53.5 (CH), 50.5 (quat), 45.1 (quat), 36.6 (quat), 35.2 (CH_2), 29.8 (CH), 29.7 (CH_3), 26.8 (CH_3), 24.0 (CH_2), 23.3 (CH_2), 21.7 (CH_3), 20.7 (CH_2), 20.2 (CH_3) ppm. MS (EI): *m*/*z* (%) = 274 (1) [M^+, $C_{17}H_{26}N_2O$], 242 (11), 177 (6), 136 (13), 71 (100). HRMS (EI): *m*/*z* calcd. for $C_{17}H_{26}N_2O$ 274.2045; found 274.2046.

2-(5-Methoxy-1,4,4,7a-tetramethyl-octahydroinden-1-yl)malononitrile (12c, minor isomer): This compound was isolated as a white solid. M.p. 105 °C. IR (KBr): $\tilde{\nu}$ = 2995, 2927, 2821, 1459, 1386, 1354, 1206, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 1 H), 3.27 (s, 3 H), 2.81 (dd, *J* = 1.9, 3.8 Hz, 1 H), 2.04 (dd, *J* = 7.3, 13.8 Hz, 1 H), 1.87−1.82 (m, 1 H), 1.69−1.66 (m, 4 H), 1.61−1.53 (m, 2 H), 1.44−1.42 (m, 1 H), 1.38 (s, 3 H), 0.94 (s, 3 H), 0.91 (s, 3 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.1 (quat), 112.5 (quat), 83.9 (CH), 57.2 (CH_3), 49.6 (quat), 46.4 (CH), 45.6 (quat), 38.2 (quat), 35.4 (CH_2), 31.5 (CH), 28.4 (CH_3), 26.6 (CH_2), 21.8 (CH_3), 21.7 (CH_3), 21.0 (CH_2), 19.9 (CH_2), 16.0 (CH_3) ppm. MS (EI): *m*/*z* (%) = 274 (3) [M^+, $C_{17}H_{26}N_2O$], 242 (2), 177 (3), 136 (6), 121 (8), 71 (100). HRMS (EI): *m*/*z* calcd. for $C_{17}H_{26}N_2O$ 274.2045; found 274.2049.

(6-Methoxy-2,5,5,8a-tetramethyl-decahydronaphthalen-1-yl)-methanol [13 (6β-methoxy)]: This compound was isolated as a white solid. M.p. 80−82 °C. IR (KBr): $\tilde{\nu}$ = 3405, 2938, 2849, 1458, 1388, 1184, 1108, 1025 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.81 (dd, *J* = 10.5, 4.6 Hz, 1 H), 3.57 (t, *J* = 9.6 Hz, 1 H), 3.32 (s, 3 H), 2.62 (dd, *J* = 11.7, 4.1 Hz, 1 H), 2.14−2.08 (m, 1 H), 1.83−1.33 (br-m, 11 H), 1.29 (pent, *J* = 4.6 Hz, 1 H), 1.05 (m, 1 H), 0.94 (s, 3 H), 0.92 (d, *J* = 7.8 Hz, 3 H), 0.83 (s, 3 H), 0.78 (dd, *J* = 11.5, 2.7 Hz, 1 H), 0.73 (s, 3 H) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 88.4 (CH), 60.8 (CH_2), 57.5 (CH_3), 56.1 CH), 55.6 (CH), 38.9 (quat), 38.1 (CH_2), 37.2 (quat), 34.4 (CH_2), 28.3 (CH), 28.2 (CH_3), 21.9 (CH_2), 17.1 (CH_3), 17.0 (CH_2), 17.2 (CH_3), 15.5 (CH_3) ppm. NOE (saturation − enhancement): δ = 3.33−2.62 (w), 1.76 (w), 0.95 (w). 2.63−3.33 (s), 1.76 (m), 0.95 (s), 0.78 (w). 2.11−3.58 (w), 1.30 (m), 0.92 (s), 1.52 (m), 1.67 (w). 1.30−2.11 (w), 1.06 (w), 0.79 (m). 0.95−0.84 (m), 0.78 (w), 0.74 (m). 0.83−0.74 (s) ppm. MS (EI): *m*/*z* (% rel. int.) = 254 (18) [M^+, $C_{16}H_{30}O_2$], 109 (100). HRMS (EI): *m*/*z*: calcd. for $C_{16}H_{30}O_2$ 254.2246; found 254.2243.

2-(7-Methoxy-3,3a,6,6,9a-pentamethyl-dodecahydro-1*H*-cyclopenta-[*a*]naphthalen-3-yl)malononitrile [15a (3β-methyl)]: This compound was isolated as a white solid. M.p. 141−142 °C. IR (KBr): $\tilde{\nu}$ = 2963, 2873, 2250, 1465, 1390, 1360, 1261, 1185, 1104, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 1 H), 3.34 (s, 3 H), 2.63 (dd, *J* = 11.5, 4.6 Hz, 1 H), 2.00−1.93 (m, 1 H), 1.84−1.66 (m, 5 H), 1.60−1.39 (m, 6 H), 1.32 (s, 3 H), 1.32−1.18 (m, 1 H), 0.96 (s, 3 H), 0.93 (s, 3 H), 0.89 (s, 3 H), 0.76 (s, 3 H), 0.69 (dd, *J* = 12.1, 2.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.8 (quat), 113.3 (quat), 88.5 (CH), 58.5 (CH), 57.6 (CH_3), 56.7 (CH), 50.6 (quat), 47.0 (quat), 39.0 (CH_2), 38.7 (quat), 36.9 (quat), 35.9 (CH_2), 35.5 (CH_2), 32.7 (CH), 28.1 (CH_2), 21.9 (CH_2), 21.3 (CH_3), 20.3 (CH_2), 18.9 (CH_2), 17.8 (CH_3), 16.3 (CH_3), 16.0 (CH_3) ppm. NOE (saturation−enhancement): δ = 3.73−1.22 (m). 2.63−0.96 (m), 0.68 (w). 1.21−3.74 (s), 0.68 (m). 0.76−0.96 (s), 0.89 (s). 0.69−2.64 (m), 1.22 (s), 0.96 (s) ppm. MS (EI): *m*/*z* (%) = 342 (13) [M^+, $C_{22}H_{34}N_2O$], 342 (42), 271 (74), 227 (100), 205 (61), 107 (94), 71 (97). HRMS (EI): *m*/*z* calcd. for $C_{22}H_{34}N_2O$ 342.2671; found 342.2667.

2-(7-Methoxy-3,3a,6,6,9a-pentamethyl-dodecahydro-1*H*-cyclopenta-[*a*]naphthalen-1-yl)malononitrile [15b (3α-methyl)]: This compound was isolated as a white solid. M.p. 188−189 °C. IR (KBr): $\tilde{\nu}$ = 2940, 2896, 2252, 1457, 1385, 1185, 1105, 1015 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 1 H), 3.34 (s, 3 H), 2.64 (dd, *J* = 11.5, 4.5 Hz, 1 H), 1.82−1.76 (m, 2 H), 1.74−1.70 (m, 2 H), 1.68−1.60 (m, 2 H), 1.57−1.49 (m, 3 H), 1.45−1.41 (m, 3 H), 1.36 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H), 0.92 (m, 1 H), 0.89 (s, 3 H), 0.76 (s, 3 H), 0.72 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.0 (quat), 112.4 (quat), 88.5 (CH), 57.6 (CH), 57.5 (CH), 56.4 (CH_3), 49.1 (quat), 46.1 (quat), 38.9 (CH_2), 38.6 (quat), 36.9 (quat), 35.8 (CH_2), 34.2 (CH_2), 31.5 (CH), 28.0 (CH_3), 21.9 (CH_2), 21.7 (CH_3), 19.3 (CH_2), 18.7 (CH_2), 17.4 (CH_3), 16.1 (CH_3), 16.0 (CH_3) ppm. NOE (saturation−enhancement): δ = 3.74−1.72 (w), 0.96 (s), 2.64−3.34 (s), 1.81 (w), 1.36 (w), 0.95 (s), 0.89 (w), 0.72 (m) ppm. MS (EI): *m*/*z* (%) = 342 (13) [M^+, $C_{22}H_{34}N_2O$], 310 (33), 270 (76), 227 (100), 107 (93), 95 (35). HRMS (EI): *m*/*z* calcd. for $C_{22}H_{34}N_2O$ 342.2671; found 342.2666.

(7-Methoxy-2,4b,8,8,10a-pentamethyl-tetradecahydrophenanthren-1-yl)methanol [16 (7β-methoxy)]: This compound was isolated as a white, insoluble solid. IR (KBr): $\tilde{\nu}$ = 3489, 2940, 1459, 1384, 1185, 1080, 970 cm^{-1}. Because of poor solubility of this product in all common organic solvents, further characterizations were carried out with its acetate derivative.

Acetylation of 16: The insoluble alcohol **10** (52 mg) was suspended under argon in a two-necked, round-bottomed flask containing dry dichloromethane (5 mL) and triethylamine (1 equiv.). The reaction mixture was cooled to 0−5 °C in an ice/water bath, and acetyl chloride (1 equiv.; Aldrich; 99%) was added dropwise with stirring. The resulting mixture was allowed to warm to room temp. and stirred at this temperature for additional 2 h, during which a clear solution formed. The organic layer was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the acetylated product **17** as a white solid.

(7-Methoxy-2,4b,8,8,10a-pentamethyl-tetradecahydrophenanthren-1-yl) Acetate [17 (7β-methoxy)]: M.p. 128 °C. IR (KBr): $\tilde{\nu}$ = 2935, 2849, 1737, 1462, 1385, 1369, 1245, 1103, 1031 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.26 (dd, *J* = 11.1, 4.8 Hz, 1 H), 4.00 (t, *J* = 9.5 Hz, 1 H), 3.33 (s, 3 H), 2.61 (dd, *J* = 11.7, 4.1 Hz, 1 H), 2.01 (s, 3 H), 1.81−1.33 (br. m, 10 H), 1.28−1.05 (m, 4 H), 0.92 (s, 3 H), 0.90 (d, *J* = 7.6 Hz, 3 H), 0.86 (s, 3 H), 0.80 (s, 3 H), 0.76 (d, *J* = 2.2 Hz, 1 H), 0.72 (s, 4 H, CH_3 + CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (quat), 88.6 (CH), 63.4 (CH_2), 60.9 (CH), 57.5 (CH_3), 55.9 (CH), 52.2 (CH), 41.6 (CH_2), 38.8 (quat), 38.3 (CH_2), 37.7 (quat), 37.3 (quat), 34.3 (CH_2), 29.1 (CH), 27.9 (CH_3), 22.2 (CH_2), 21.1 (CH_3), 18.0 (CH_3), 17.6 (CH_2), 16.4 (CH_2), 16.3 (CH_3), 15.9 (CH_3), 15.6 (CH_3) ppm. NOE (saturation−enhancement): δ = 3.99−0.86 (s), 0.90 (m), 2.61−0.92 (s), 0.76 (m). 2.01−0.90 (s). 0.90−0.86 (s). 0.80−0.72 (m). 0.73−0.80 (s) ppm. MS (EI): *m*/*z* (%) = 364 (9.56) [M^+, $C_{23}H_{40}O_3$], 332 (30), 221 (73), 189 (100), 135 (47), 123 (43), 109 (58), 81 (38). HRMS (EI): *m*/*z* calcd. for $C_{23}H_{40}O_3$ 364.2977; found 364.2981.

Supporting Information: ^1H and ^{13}C NMR spectra for products **8**−**17**.

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[11] Relative stereochemistries are assigned by NOE/NOESY experiments. The α/β terminology used in this paper is adopted from the steroid convention (i.e., α means below and β above the paper plane).

[12] Yields given are based on isolated amounts after purification.

[13] Diastereomeric ratios were determined by ^{13}C NMR analysis of the isomer mixture and are in accordance with isolated amounts after HPLC separation.

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