Investigations of Cascade Cyclizations of Terpenoid Polyalkenes via Radical Cations. A Biomimetic-type Synthesis of $\pm$-3-Hydroxy-spongian-16-one

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Abstract: A short and efficient synthesis of the tetracyclic oxygenated diterpene analog of 8, i.e., of 3-hydroxy-spongian-16-one (7), has been achieved in only five steps via a cascade cyclization of the functionalized terpenoid polyalkene 4. Photoinduced electron transfer serves as the pivotal step for selectively creating a radical cation intermediate. Such polycyclizations are radical-driven upon regio- and stereoselective trapping of the radical cation by a nucleophile, such as water in the present case. The overall reaction sequence mimics the non-oxidative biosynthesis of terpenes.

Key words: photoinduced electron transfer, radical cation, biomimetic synthesis, photochemistry, 3-hydroxy-spongian-16-one, radical cyclization, natural products

Oxygenated tetracyclic diterpenes from marine sponges, such as spongian-16-one (8) from the sponge Dictyodendrilla cavernosa,1 found in waters of the Eastern seaboard of Australia and New Zealand, represent an important class of natural products due to their antimicrobial properties against leukaemia cells and herpes simplex virus type 1.2 A synthesis of $\pm$-8 has been reported by Pattenden and co-workers,3 who used a radical-driven polycyclization step to build up the basic tetracyclic framework of the target compound (for earlier synthetic activities related to this field, see citations 6 and 7 in ref. 3). We report herein a short biomimetic-type synthesis of the 3-hydroxyl analog of 8, i.e., of $\pm$-3-hydroxy-spongian-16-one (7), which can be considered as a straight synthetic precursor of 8 if access to the latter compound would specifically be required. Photoinduced electron transfer (PET) served in the pivotal step to initiate the highly stereo- and regioselective cyclization and functionalization of the acyclic polyalkene terpenoid 4.

Isoprenoid polypeptide radicals, formed by anti-Markovnikov addition of water to their parent radical cations, which are readily accessible via PET, undergo cascade cyclizations.4 More recent investigations along these lines revealed straightforward synthetic applications, i.e., ready access to a steroid product in high enantiomeric purity5 and to the naturally abundant stypoldione in racemic form.6 In the present case, PET-triggered cyclization of 4 yields 7 as the major photoproduct in which 7 stereogenic centers are created in a single photochemical step (Scheme). This result is highly remarkable in view of the 256 theoretically possible stereoisomers, which could form in such a process. Spontaneous folding of the polyalkene chain in all-pre-chair conformation, as depicted (4 $\rightarrow$ 5) en route to 7, is in analogy to earlier observations5 in our preferred notion concerning the initial mechanistic pathways (Scheme).

Scheme

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steps. Interestingly, strong evidence for an analogous biomimetic process, albeit carbocationically driven, is found for the stepwise cyclization of 2,3-oxidosqualene to prosterol.\textsuperscript{7} The regio- and stereoselective addition of water including the cyclization and termination events are mechanistically presumed for PET-initiated polycyclizations, again in analogy to our earlier findings,\textsuperscript{8–10} to occur in the following order: a) water addition to the radical cation site of 5, b) radical cyclization to 6 and c) termination of the cyclization cascade by either hydrogen atom transfer to the C(13) radical in 6 or its reduction to the parent anion followed by protonation (→ 7). The latter termination mechanism seems, however, to be favorable under the applied reaction conditions when considering the relatively low reduction potential of an α-carbonyl radical such as the C(13) radical in 6.

The synthesis starts with the conjugate addition of (E,E)-farnesyltri-n-butylstannane (1) to α-methylene-γ-butyro-lactone (2) upon treatment of 1 with n-BuLi, Cul, LiBr and TMSCl in THF by adopting a procedure for Michael additions of allylic ligands to a variety of α,β-unsaturated ketones with allylic copper reagents.\textsuperscript{11} The coupling product 3 was isolated in 92% yield after chromatography. (E,E)-Farnesyltri-n-butylstannane (1) was readily prepared in 90% yield by treatment of (E,E)-farnesylbromide with tri-n-butylstannyl chloride and magnesium turnings in THF adopting a procedure reported for a related example.\textsuperscript{12} Lactone 3 can then be converted to the terpenoid photoeduct 4 in good yields by following known procedures for analogous functional group transformations [ref. 13 for (a) and ref. 14 for (b) in the Scheme]. (E,E)-Farnesylmethyl-4,5-dihydro-2(3H)-furanone (4) was first treated with lithium hexamethyldisilazide and phenylselene nyl bromide to introduce a phenylene group in α-position of the lactone carbonyl in 68% yield. Subsequent oxidation and in situ elimination of the seleno moiety with a mixture of m-chloroperbenzoic acid and pyridine afforded the (E,E)-farnesylmethyl-2(5H)-furanone (4) in 52% yield. With compound 4 in hand, the pivotal photochemical step was achieved upon irradiation of 4 \((\lambda_{\text{max}} = 300 \text{ nm}, \text{Rayonet reactor})\) in MeCN-H\textsubscript{2}O (10:1) at −25°C together with the electron acceptor couple 1,4-dicyanotetramethylbenzene/biphenyl in catalytic amount (2 mol%) to afford 7 as the major photoproduct in 23% yield after purification. MeCN-H\textsubscript{2}O is routinely employed as a polar solvent mixture for such PET transformations in order to facilitate the electron transfer; at the same time the co-solvent water acts as the nucleophile to trap the intermediate radical cation in 5 (→ 6). The radical saturation step 6 → 7 is, as mentioned earlier, the result of a reduction/protonation sequence as a consequence of the estimated relatively low reduction potential of the C(13) radical in 6. Notably, protonation occurs in the present example exclusively from the less hindered exo face affording 7 with cis junction of the CD rings. The structure of 7 was unambiguously determined by NOE and X-ray analyses.\textsuperscript{13} The fact that no mono- and bicyclic products have been found after photochemical transformation of 4 points to an exclusive oxidation of the terminal C=C bond of 4 giving rise to the formation of the intermediate radical cation 5. The two ‘inner’ C=C bonds are seemingly efficiently shielded from the radical acceptor, i.e., from the oxidized biphenyl (= biphenyl\textsuperscript{+}; for a discussion of the radical acceptor mechanism of the 1,4-dicyanotetramethylbenzene/biphenyl couple, see ref. 16). Further, the 2(SH)-furanone moiety can by no means be oxidized by biphenyl\textsuperscript{+} because of its high lying oxidation potential.

In summary, this synthesis of (±)-3-hydroxy-spongian-16-one (7) in only five steps demonstrates the effectiveness of PET-induced cascade polycyclizations as the pivotal step for the synthesis of polycyclic (natural) products bearing an oxygen function at C(3). In such a cyclization event, 7 asymmetric centers emerge with well-defined and predictable stereochemistry in a single photocatalytic step. In contrast to the usually lengthy preparation of the starting materials for pure radical-driven polycyclizations, as e.g., the example in ref. 3, the precursors for radical cation-initiated cyclization cascades, being terpenoid polyenes, are more readily available.

All reactions were carried out under Ar atm, the purification of reaction products was carried out by flash column chromatography using Sepapak-FPGC glass columns from Kronlab with different I.D. and length, dry packed with silica gel (0.063–0.200 mm). IR spectra were recorded on a FT-IR-spectrometer Perkin–Elmer 1600 Series. Mass spectra were recorded on a Finnigan MAT 311A or 8230.\textsuperscript{13} H and \textsuperscript{13}C NMR spectra were recorded using Bruker AC-250 or AM-400 instruments. NOE: abbreviations: s (strong), m (medium) and w (weak).

\textbf{(E,E)-Farnesyltri-n-butylstannane (1)}

To a stirred suspension of magnesium turnings (1.06 g, 44 mmol) in THF (12 mL), a solution containing (E,E)-farnesylbromide (11.5 g, 0.04 mol) and tri-n-butylstannyl chloride (6.5 g, 0.02 mol) in THF (20 mL) was added dropwise at 0°C. The reaction was heated to reflux for 2 h, cooled to 0°C in an ice-bath, and quenched with sat. NH\textsubscript{4}Cl (10 mL). After filtration and removal of most of the THF in vacuo, Et\textsubscript{2}O (40 mL) was added to the residue and the organic phase was separated, washed with H\textsubscript{2}O (2 × 30 mL), once with brine (30 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and evaporated under reduced pressure. Upon chromatography (column: I.D. 52 mm, length 1121 mm; CH\textsubscript{3}Cl–pentane, 40:1) of the residue, 1 was obtained as a colorless oil (9.2 g, 18.4 mmol, 90%).

1H NMR (250 MHz, CDCl\textsubscript{3}); δ = 5.35 (s, 1H, J = 8.9 Hz), 5.11–5.05 (m, 2H), 2.05–1.97 (m, 8H), 1.67 (s, 3H), 1.67–1.63 (m, 2H), 1.59 (s, 6H), 1.56 (s, 3H), 1.50–1.21 (m, 12H), 0.91–0.88 (m, 6H), 0.86–0.84 (m, 9H).

13C NMR (62.9 MHz, CDCl\textsubscript{3}); δ = 134.72 (C\textsubscript{7}), 131.17 (C\textsubscript{7}), 129.23 (C\textsubscript{7}), 124.57 (CH), 124.45 (CH), 122.83 (CH), 39.91 (CH\textsubscript{3}), 39.80 (CH\textsubscript{3}), 29.24 (CH\textsubscript{2}), 27.40 (CH\textsubscript{2}), 26.77 (CH\textsubscript{3}), 26.34 (CH\textsubscript{3}), 25.67 (CH\textsubscript{3}), 17.65 (CH\textsubscript{3}), 15.95 (CH\textsubscript{3}), 13.70 (CH\textsubscript{2}), 10.65 (CH\textsubscript{2}), 9.39 (CH\textsubscript{3}).

MS: m/z (%) = 496 (7, M\textsuperscript{+}, C\textsubscript{27}H\textsubscript{52}Sn), 439 (6), 325 (2), 291 (100), 235 (73), 179 (64), 121 (20), 81 (13), 69 (56), 41 (30).

HRMS: m/z calcd for C\textsubscript{27}H\textsubscript{52}Sn: 496.3090. Found: 496.3089.

\textbf{(E,E)-Farnesylmethyl-4,5-dihydro-2(3H)-furanone (3)}

A solution of CuI (7.5 g, 37.5 mmol) and anhyd LiBr (3.4 g, 37.5 mmol) in THF (50 mL) was stirred for 5 min and then cooled to −78°C. Concurrently, n-BuLi (15%, 25 mL, 37.5 mmol) was added

\textbf{(±)-3-Hydroxy-spongian-16-one (7)}

\(\text{C}_{37} \text{H}_{72} \text{O}_{5} \)
dropwise to a solution of I (18.75 g, 37.5 mmol) in THF (50 mL) and stirred for 15 min at −78 °C. This solution was then transferred to the CuI/LiBr solution (−78 °C) to yield a tan solution. TMSCl (4.01 mL, 31.6 mmol) was added followed by the addition of α-methylene-γ-butyrolactone (2, 2.80 mL, 31.6 mmol). The mixture was stirred for 30 min, and the reaction was quenched with sat. NH₄Cl (80 mL). After extraction with Et₂O (3 × 100 mL), the combined organic layers were dried (Na₂SO₄). The solvent was removed in vacuo and the residue was chromatographed (column: I. D. 52 mm, length 1121 mm; Et₂O–pentane, 15:1) to give lactone 3 (8.6 g, 28.5 mmol, 92%) as a colorless oil.

IR (film): ν = 1781 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 5.10−5.05 (m, 3H), 4.34−4.09 (m, 2H), 2.52−2.32 (m, 2H), 2.09−1.88 (m, 12H), 1.66 (s, 1H), 1.64 (s, 3H), 1.58 (s, 9H).

13C NMR (62.9 MHz, CDCl₃): δ = 179.50 (C₆), 136.70 (C₅), 135.26 (C₄), 131.23 (C₃), 124.26 (CH), 123.98 (CH), 122.74 (CH), 66.35 (CH₃), 39.65 (CH₃), 39.61 (CH₃), 38.57 (CH₃), 30.39 (CH₃), 28.70 (CH₃), 26.69 (CH₃), 26.64 (CH₃), 25.61 (CH₃), 25.50 (CH₃), 17.60 (CH₃), 15.99 (CH₃), 15.94 (CH₃).

MS: m/z (%) = 304 (15, M⁺, C₂₀H₃₂O₂), 289 (1), 273 (10), 235 (8), 219 (13), 115 (100), 101 (100), 55 (24), 41 (64).

HRMS: m/z calcd for C₂₀H₃₂O₂: 304.2395. Found: 304.2394.

(E,E)-Farnesylmethyl-2(5H)-furanone (4)

Lactone 3 (7.5 g, 24.6 mmol) in THF (37 mL) was added to a THF solution (200 mL) containing lithium hexamethyldisilazide [prepared from bis(trimethylsilyl)amine (7.15 g, 44.3 mmol) and n-BuLi (15%, 32.4 mL, 49 mmol)] at −78 °C. After 25 min, phenylethenyl bromide (11.56 g, 49 mmol) in THF (50 mL) was added to this solution and immediately thereafter the mixture was quenched with H₂O (200 mL). The reaction mixture was poured into Et₂O (500 mL) and the organic phase was separated, washed sequentially with H₂O (3 × 80 mL), Na₂CO₃ (80 mL) and brine (80 mL), then dried (Na₂SO₄) and concentrated in vacuo. The residue was chromatographed (column: I. D. 37 mm, length 539 mm; Et₂O–pentane, 15:1) to afford the α-phenylseleno lactone derivative of 3 (7.6 g, 16.5 mmol, 68%) as a colorless oil.

The α-phenylseleno lactone derivative of 3 (7.6 g, 16.5 mmol) was dissolved in EtOAc (400 mL) prior to its treatment with pyridine (5.7 mL, 0.07 mol) and m-CPBA (8.6 g, 0.05 mol). The mixture was stirred for 20 min at rt, washed with H₂O (3 × 100 mL), dried (Na₂SO₄), concentrated in vacuo, and chromatographed (column: I. D. 37 mm, length 539 mm; Et₂O–pentane, 10:1) to give 4 (2.5 g, 8.5 mmol, 52%) as a colorless oil.

IR (film): ν = 1755 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.07 (t, 1H, J = 1.6 Hz), 5.08−5.05 (m, 3H), 4.72 (d, 2H, J = 1.6 Hz), 2.30−2.25 (m, 4H), 2.04−1.93 (m, 8H), 1.66 (s, 3H), 1.64 (s, 3H), 1.56 (s, 6H).

13C NMR (100 MHz, CDCl₃): δ = 174.32 (C₆), 144.26 (CH), 136.75 (C₅), 135.30 (C₄), 133.92 (C₃), 131.23 (C₂), 124.25 (CH), 123.97 (CH), 122.59 (CH), 70.04 (CH₂), 39.66 (CH₃), 39.61 (CH₃), 38.57 (CH₃), 30.39 (CH₃), 28.70 (CH₃), 26.69 (CH₃), 26.64 (CH₃), 25.61 (CH₃), 25.50 (CH₃), 17.60 (CH₃), 15.99 (CH₃), 15.94 (CH₃).

MS: m/z (%) = 320 (36, M⁺, C₂₀H₃₂O₃), 305 (60), 287 (76), 259 (18), 207 (100), 189 (87), 135 (61), 121 (70), 107 (65), 95 (64), 81 (67), 67 (58), 57 (70), 41 (92).


References

(9) Xing, X. Ph. D. Thesis; Max-Planck-Institut für Strahlenchemie/University of Essen; Germany, 1997.
(15) Goeller, F. Ph. D. Thesis; Max-Planck-Institut für Strahlenchemie/University of Essen, in progress.