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Oxidative cyclization of a *seco*-cladiellane diterpenoid

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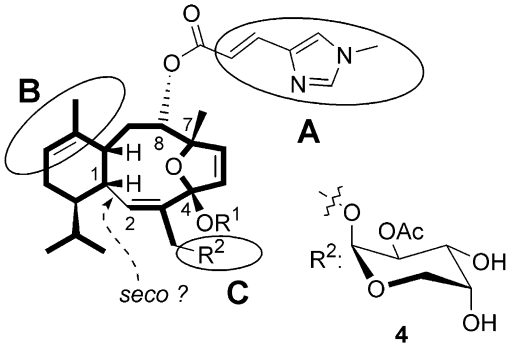
Abstract—A short and efficient synthesis of a diterpenoid with a 1,2-*seco*-cladiellane carbon skeleton is described, starting from geraniol and carvone. One-step oxidative cyclization with a $RuO_2/NaIO_4$ system leads to two diastereomeric, bicyclic triols, which contain six stereogenic centers and will be helpful in the synthesis of eleutherobin. The stereochemical outcome of this cyclization has been determined by X-ray analysis.

1. Introduction

In 1997 Fenical et al. reported the marine natural product eleutherobin, isolated from the soft coral *Eleutherobia* sp. (**1**, Fig. 1).[1] Eleutherobin and the sarcodictyins A (**2**) and B (**3**)[2] have been shown to possess antimitotic activity and to stabilize microtubuli in a similar way to paclitaxel.[3] Currently, there are only two completed total syntheses of eleutherobin (**1**) by Nicolaou et al.[4] and by Danishefsky and co-workers[5] each of which needs about 25 single conversions. Different groups have isolated and synthesized eleutherobin and sarcodictyin analogs.[6,7]

Recently, Andersen and co-workers have shown that the dihydrofuran and the cyclohexene double bonds may be hydrogenated with tolerable loss of activity.[8] This encouraged us to investigate the synthesis of saturated analogs. We wish to report on an efficient approach to a cladiellane, which is cut between C1 and C2 and, therefore, named 1,2-*seco*-cladiellane. It was our hypothesis that the C_{20} skeleton should be accessible starting from two C_{10} building blocks.

Introduction of the tetrahydrofuran system was envisaged in a one-step oxidative cyclization. Moreover, we had to learn something about the stereochemical outcome of that oxidation.



1: Eleutherobin (R^1 = Me, R^2 = **4**)
2: Sarcodictyin A (R^1 = H, R^2 = CO_2Me)
3: Sarcodictyin B (R^1 = H, R^2 = CO_2Et)

Figure 1. Structures of eleutherobin (**1**) and sarcodictyins A (**2**) and B (**3**) with their ABC pharmacophor.

2. Results and discussion

Cyclizations of 1,5-dienes to tetrahydrofurans using permanganate have been described in various natural products syntheses.[9] However, the closely related reaction with $RuO_2/NaIO_4$, a system that was first described by Djerassi and co-workers,[10] has only rarely been used, although better yields should be expected.[11]

In a first experiment we treated geranyl acetate (**5**) with $KMnO_4$ under conditions first described by Klein and Rojahn.[12] We found that the desired tetrahydrofuran **6** was formed in only 35% isolable yield. As major side products, hemiketals **7** and **8** were formed in 10% and 5% yield (Scheme 1). The hitherto unreported formation

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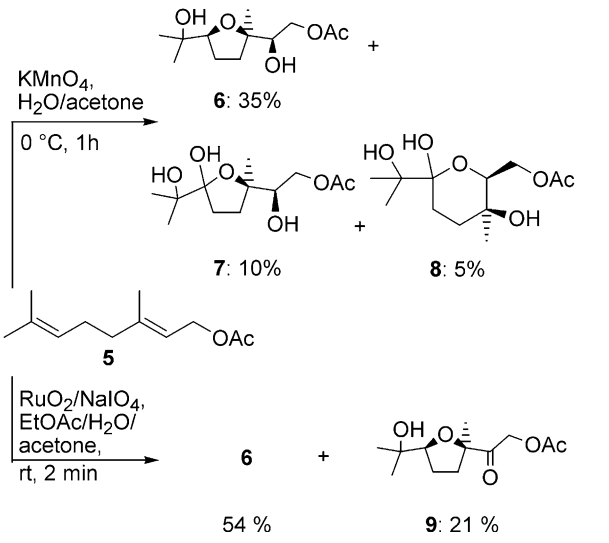


Scheme 1. Oxidative cyclization with $KMnO_4$ and $RuO_2/NaIO_4$.

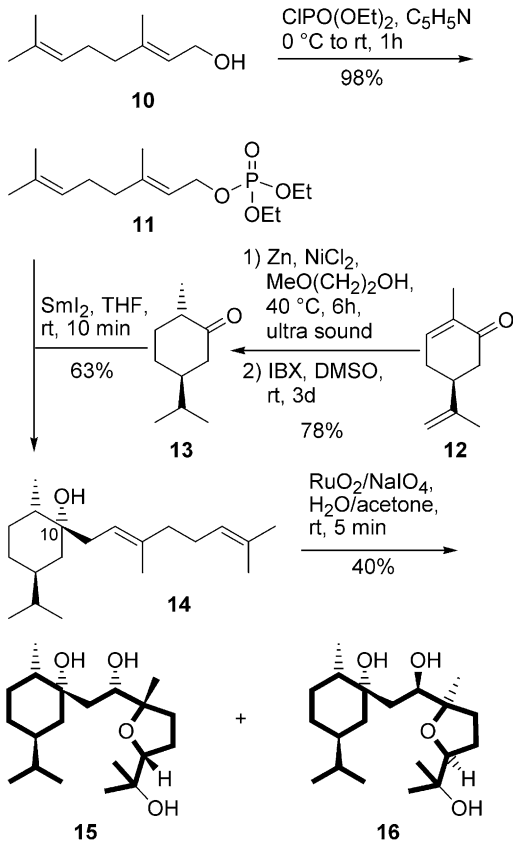
of **7** and **8** can be explained by initial dihydroxylation of the terminal double bond of geranyl acetate, followed by oxidation to the acyloin. Subsequent dihydroxylation of the allyl acetate sets the stage for the two possibilities of cyclization to the tetrahydrofuran resp. tetrahydropyran rings. In each case only one diastereomer was formed. The stereochemistry of the generated anomeric carbon atom has not been elucidated.

A much cleaner reaction was observed on oxidative cyclization of **5** with $RuO_2/NaIO_4$. Under the conditions described by Sica and co-workers the desired product **6** was isolated in satisfying 54% yield, along with 21% of overoxidized tetrahydrofuran **9** (Scheme 1).[13] The relative stereochemistry of **6** has been determined by X-ray analysis.

We next turned to the diterpenoid case. Our synthesis of the cyclization precursor **14** starts with the reduction of (*S*)-(+)-carvone (**12**) to tetrahydrocarvone (**13**), which is possible stereoselectively, although not completely chemoselectively, by the $Zn/NiCl_2$-system developed by Petrier and Luche (Scheme 2).[14] Overreduction occurs to a certain extent and makes re-oxidation of the alcohol necessary. SmI_2-mediated reductive coupling of **13** with allylic phosphate **11**, synthesized in quantitative yield from geraniol (**10**), by a method described by Butsugan and co-workers,[15] led to the *seco*-cladiellane **14** in 63% yield. Interestingly, prolonged reaction times in this step led to a decrease in isolated yield. S_N2-selective SmI_2-induced Barbier-type reactions have been used in a number of natural products syntheses. However, the method employing phosphates as coupling reagents is less common.[16]

seco-Cladiellane **14** with *S*-configuration at C-10 is the only diastereomer formed in this reaction. Later, we could show that nucleophilic S_N2 attack occurred from the *si* face of the carbonyl group.

Treatment of *seco*-cladiellane **14** with the $RuO_2/NaIO_4$ system finally led to oxidized and cyclized, diastereo-



Scheme 2. Synthesis of *seco*-cladiellane **14** and biomimetic, oxidative cyclization to **15** and **16**.

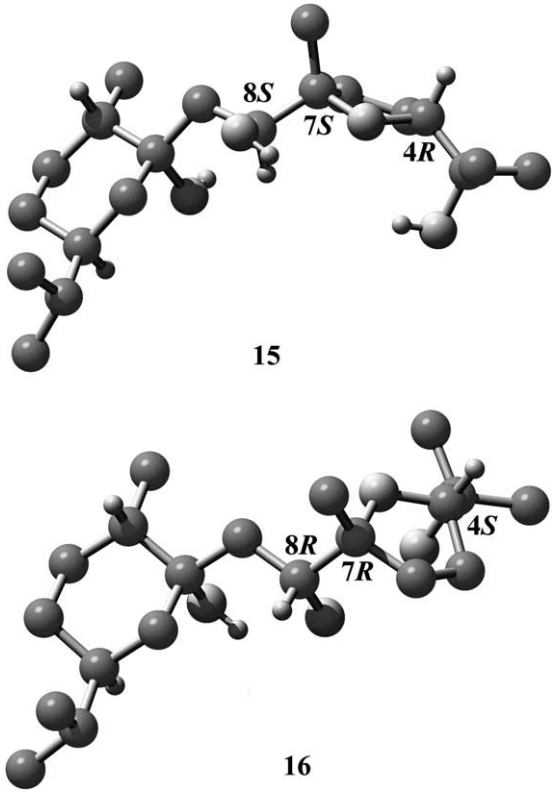


Figure 2. SCHAKAL plots of **15** and **16** showing the configuration of the newly formed stereocenters. H-atoms at nonstereogenic centers are omitted for clarity.

meric triols **15** and **16** along with minor amounts of diastereomeric overoxidized products (Scheme 2).[17] Diastereomers **15** and **16** are formed as an easily separable 1:1 mixture in 40% combined yield.

We were able to obtain X-ray data of both diastereomers, which allowed us to assign their absolute configurations.[18] Both diastereomers show *syn* configuration at the tetrahydrofuran moiety. The newly formed stereocenters possess 4*R*, 7*S*, 8*S* configuration in **15** and 4*S*, 7*R*,8*R* in **16** (Fig. 2). The stereochemical outcome of this reaction is consistent with mechanistic considerations.[13,19]

In summary, we have shown that a 1,2-*seco*-cladiellane may be easily synthesized from geraniol in two steps with an overall yield of 62%. We have also shown that the tetrahydrofuran ring, three stereocenters, as well as two of the oxygen atoms present in sarcodictyins may be introduced in a single step.

A pharmacophor consisting of three subunits A–C has been proposed by Ojima et al. (Fig. 1).[20] Open-ring 1,2-*seco*-cladiellanes derived from **15** and **16** will be useful in testing that pharmacophor model.

Acknowledgements

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17. Selected physical and spectroscopical data. **15**: Mp 115.1–115.3 °C. $[\alpha]_D^{20}$ −20 (*c* 1.9 mg/mL in $CHCl_3$). IR (KBr) $\tilde{\nu}$ = 3447 (s, br), 2955 (s), 2924 (s), 2872 (m), 1636 (m, br), 1466 (m), 1381 (m), 1368 (m), 1344 (w), 1319 (w), 1278 (w), 1241 (w), 1184 (w), 1150 (w), 1099 (m), 1062 (m), 1021 (w), 983 (w), 951 (w), 920 (w), 884 (w), 850 (w), 798 (w), 616 (w), 530 (w). UV/vis ($CHCl_3$): $\lambda_{max}(\varepsilon)$ = 207 nm (8136 mol^{-1} dm^3 cm^{-1}), 262 (11740 mol^{-1} dm^3 cm^{-1}), 285 (12736 mol^{-1} dm^3 cm^{-1}). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (t, ^3J = 6.96 Hz, 1H), 3.75 (dd, ^3J = 9.34 Hz, ^3J = 1.47 Hz, 1H), 2.2 (s, br, 3H), 1.97–1.88 (m, 3H), 1.78 (td, ^2J = 13.55 Hz, ^3J = 2.56 Hz, 1H), 1.69–1.62 (m, 3H), 1.53 (dd, ^2J = 14.65 Hz, ^3J = 9.34 Hz, 1H), 1.49–1.27 (m, 5H), 1.25 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 1.13 (td, ^2J = 13.55 Hz, ^3J = 2.56 Hz, 1H), 0.92–0.89 (m, 1H), 0.91 (d, ^3J = 6.23 Hz, 3H), 0.86 (d, ^3J = 6.59 Hz, 3H), 0.84 (d, ^3J = 6.96 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 86.1, 85.4, 74.4, 73.1, 71.5, 43.1, 42.7, 40.2, 38.8, 34.8, 32.6, 31.1, 28.9, 27.5, 26.6, 25, 21.0, 20.1, 19.4, 15.5. MS (FAB^+): *m/z* (%): 686 (3) $[2M+H]^+$, 343 (23) $[M+H]^+$, 325 (14), 307 (47), 155 (29), 143 (12), 95 (14), 75 (20), 71 (14), 57 (15). HRFABMS $C_{20}H_{39}O_4$ $[M+H]^+$: calcd 343.2848; found 343.2821. **16**: Mp 92–95.6 °C. $[\alpha]_D^{20}$ +8 (*c* 1.6 mg/mL in $CHCl_3$). IR (film) $\tilde{\nu}$ = 3420 (s, br), 2967 (s), 2931 (s), 2873 (s), 1771 (w), 1634 (w), 1464 (m), 1416 (w), 1367 (m), 1249 (w), 1166 (m), 1109 (m), 1083 (m),1028 (w), 994 (w), 949 (w), 888 (w), 788 (w), 552 (w). ^1H NMR (400 MHz,

$CDCl_3$): δ = 3.88 (dd, ^3J = 9.89 Hz, ^3J = 1.47 Hz, 1H), 3.87 (t, ^3J = 6.96 Hz, 1H), 2.82–2.61 (s, br, 3H), 2.1–1.90 (m, 5H), 1.66 (td,^2J = 12.82 Hz, ^3J = 2.75 Hz, 1H), 1.6 (ddd, ^2J = 14.65 Hz, ^3J = 8.06 Hz, ^3J = 6.96 Hz, 1H), 1.50–1.36 (m, 3H), 1.33 (m, 1H), 1.26 (m, 2H), 1.26 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 0.95–0.89 (m, 2H), 0.91 (d, ^3J = 6.23 Hz, 3H), 0.88 (d, ^3J = 6.23 Hz, 3H), 0.85 (d, ^3J = 6.23 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.5, 85.5, 73.8, 73.6, 71.8, 40.8, 40.0, 40, 38.6, 34.6, 32.6, 30.6, 28.7, 27.7, 26.4, 25.2, 22.3, 20.1, 19.3, 15. MS (FAB$^+$): *m/z* (%): 707 (3) $[2M+Na]^+$, 686 (2) $[2M+H]^+$, 365 (48) $[M+Na]^+$, 343 (26) $[M+H]^+$, 325 (30), 323 (12), 308 (21), 301 (100), 263 (12), 173 (17), 155 (78), 154 (11), 151 (13), 143 (61), 137 (31), 136 (13), 127 (21), 125 (24), 111 (11), 109 (17), 107 (12), 97 (10), 95 (32), 85 (18), 83 (13), 81 (28), 73 (12), 71 (40), 69 (25), 67 (11), 55 (25). HRFABMS $C_{20}H_{39}O_4$ $[M+H]^+$: calcd 343.2848; found 343.2853.

18. CCDC-256464 (**15**) and CCDC-256465 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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