ChemComm

Total synthesis of (+)-rottnestol†

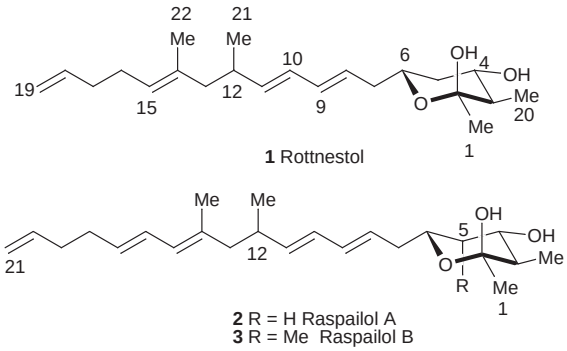
Ivona R. Czuba and Mark A. Rizzacasa*

School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia.
E-mail: m.rizzacasa@chemistry.unimelb.edu.au

Received (in Cambridge, UK) 2nd June 1999, Accepted 18th June 1999

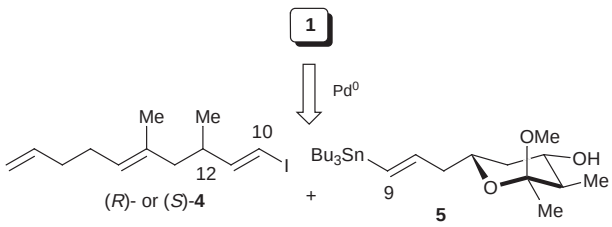
The first total synthesis of the marine metabolite (+)-rottnestol is described.

Marine sponges provide a large range of novel and bioactive metabolites that generally fall into defined chemotaxonomic groups. Recently, some tetrahydropyran containing secondary metabolites have been isolated from sponges that are chemically quite different to compounds that were previously isolated from the same sources. Chemical investigation of the sponge genus *Haliclona* sp., collected around Rottnest Island off the coast of Western Australia, yielded the hemiketal rottnestol (**1**).[1] The structure of **1** was determined using NMR techniques and by comparison to the related compounds, the raspailols A (**2**) and



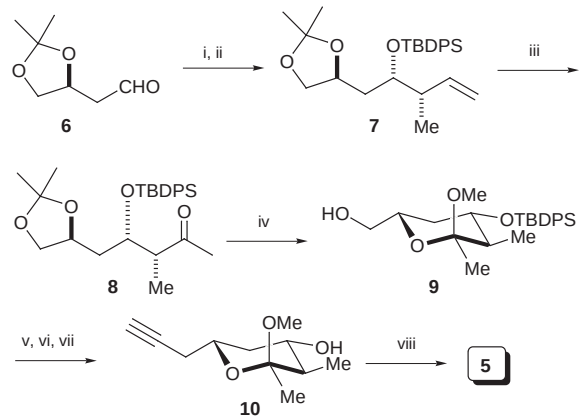
B (**3**), which were isolated from the sponge *Raspailia* sp. and possess antibiotic activity.[2] However, only small amounts of **1**–**3** were isolated which precluded oxidative degradation to determine the absolute configuration at C12.[1,2] We now report the first total synthesis of each of the possible C12 epimers of **1** which allowed for the assignment of the absolute configuration of this compound.

In designing a synthetic approach to both C12 epimers of **1**, we noted that a pivotal retrosynthetic bond cleavage would be between C9–C10. To generate this linkage, we elected to utilise a Stille cross-coupling protocol because of its remarkable success in constructing diene systems.[3,4] Therefore, coupling between an optically pure C10–C19 fragment **4** and a suitable vinylstannane such as **5** could provide each of the C12 epimers of **1** in a highly convergent manner.

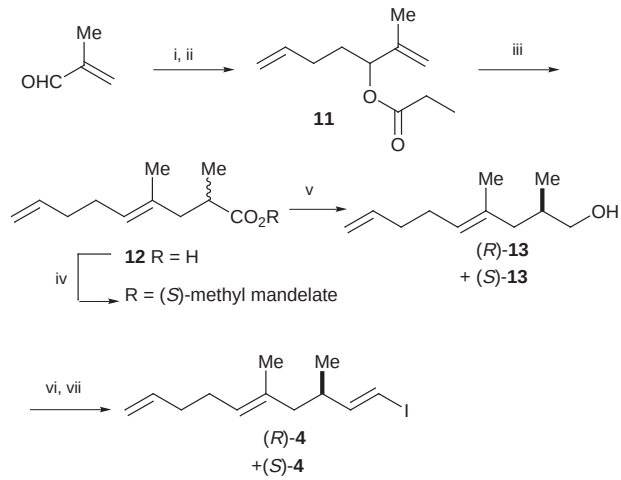


Our approach to the C12 isomers of **1** began with the synthesis of pyran fragment **5** as outlined in Scheme 1. Brown crotylmetallation[5] of the (*S*)-malic acid derived aldehyde **6**[6] followed by silylation provided alkene **7** in good yield. Wacker oxidation[7] using catalytic palladium chloride gave the ketone **8** which upon treatment with camphorsulfonic acid in MeOH afforded the pyran **9** as one anomer. Conversion of the alcohol **9** into an unstable triflate followed by lithium acetylide displacement and silyl group removal provided acetylene **10**. Radical hydrostannylation[8] of **10** in boiling benzene then afforded stannane **5** ready for Stille coupling.

The synthesis of both enantiomers of the sidechain vinyl iodide **4** is outlined in Scheme 2. Addition of but-3-enylmagnesium bromide to methacrolein gave the known allylic alcohol[9]

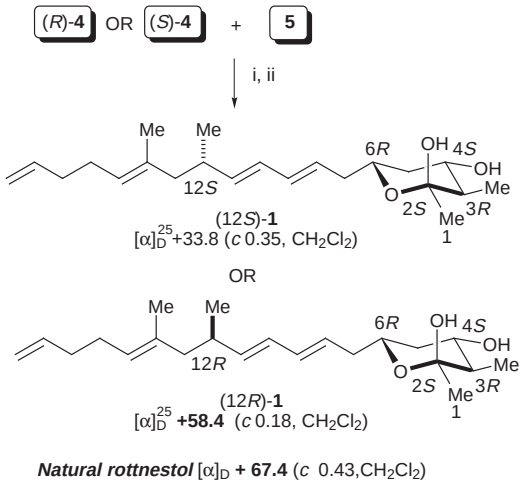


Scheme 1 *Reagents and conditions*: (i) (+)-Ipc_2B-(*Z*)-crotyl then NaOH, H_2O_2 (76%) (ii) TBDPSCl, imidazole, DMF (85%); (iii) 20 mol% $PdCl_2$, 1.1 equiv. CuCl, O_2, aq. DMF, 50 °C (85%); (iv) 20 mol% CSA, MeOH, RT, 3 h (72%); (v) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (vi) LiC≡CTMS, THF–HMPA, −78 to 0 °C; (vii) TBAF·$3H_2O$, THF, RT (71% for 3 steps); (viii) 1.1 equiv. Bu_3SnH, 10 mol% AlBN, benzene, reflux, 2 h (54%). Ipc = Isopinocampheyl.



Scheme 2 *Reagents and conditions*: (i) CH_2=$CHCH_2CH_2MgBr$, Et_2O (65%); (ii) propionyl chloride, pyridine, CH_2Cl_2 (91%); (iii), LDA, THF–HMPA, TBSCl, −78 °C to rt, then aq. HCl (84%); (iv) (*S*)-methyl mandelate, DCC, 10 mol% DMAP, normal phase HPLC separation (86%); (v) $LiAlH_4$, Et_2O (86%); (vi) Dess–Martin reagent, CH_2Cl_2 (100%) (vii) 7.5 equiv. $CrCl_2$, 1.9 equiv. CHI_3, 6:1 dioxane–THF, rt (71%).

† Dedicated to Professor Robert E. Ireland on the occasion of his 70th birthday.



Natural rottnestol $[\alpha]_D$ **+ 67.4** (*c* 0.43,CH_2Cl_2)

Scheme 3 *Reagents and conditions*: (i) 10 mol% $Pd(MeCN)_2Cl_2$, i-Pr_2NEt, DMF, rt (54–62%); (ii) 5% aq. HCl, THF, 0 °C (55–66%).

which was propionylated to provide ester **11**. Ireland–Claisen rearrangement[10,11] of **11** gave the racemic acid **12** in high yield upon acidic work-up. Resolution of the α-methyl chiral acid **12** was achieved by conversion to the corresponding (*S*)-mandelate esters followed by HPLC separation of the diastereoisomeric (*R*,*S*)- and (*S*,*S*)-mandelates.[11] Reduction of each mandelate ester then gave the optically pure alcohols (*R*)-**13** {$[\alpha]_D^{25}$ +6.5 (*c* 1.0, $CHCl_3$)} and (*S*)-**13** {$[\alpha]_D^{25}$ −6.6 (*c* 1.0, $CHCl_3$)} and the absolute configurations of each were determined by the ^{1}H NMR analysis of the derived (*S*)-MTPA esters.[12,13]‡ Dess–Martin oxidation[14] of (*R*)- and (*S*)-**13** followed by vinyliodination[15] then provided iodides (*R*)- and (*S*)-**4**.

Palladium-mediated coupling of (*R*)- or (*S*)-**4** with stannane **5** proceeded smoothly§ and subsequent acid hydrolysis afforded (12*R*)- and (12*S*)-**1** respectively (Scheme 3). Not surprisingly, (12*R*)- and (12*S*)-**1** could not be differentiated by either ^{1}H or ^{13}C NMR spectroscopy and both were identical to rottnestol in all respects apart from the optical rotation of (12*S*)-**1**.¶ As shown in Scheme 3, (12*R*)-**1** possesses a rotation with the same sign and similar value to that of natural rottnestol[1] while (12S)-**1** had a much lower value. We therefore propose the absolute configuration of rottnestol (**1**) to be 2*S*,3*R*,4*S*,6*R*,12*R*. Application of this approach to the synthesis of the raspailols is now underway.

We thank Dr M. Boyd and Dr J. Beutler of the NCI Maryland, USA for the generous gift of natural rottnestol (**1**) for TLC comparison and copies of the ^{1}H and ^{13}C NMR spectra. This work was financially supported by the Australian Research Council.

Notes and references

‡ For the (*R*,*S*)-MTPA ester (derived from (*R*)-**13** and (*S*)-MTPA) the C1 methylene protons appear as a doublet at δ 4.14 (J = 5.2 Hz) while for the (*S*,*S*)-MTPA ester the same protons appear as well separated doublets of doublets at δ 4.03 (J = 10.8, 6.4 Hz) and 4.24 (J = 10.8, 4.8 Hz): see refs. 12 and 13.

§ Interestingly, the C4-TBDPS ether of **5** and (±)-**4** failed to undergo cross coupling under a variety of conditions.

¶ *Selected data* for (12*R*)- and (12*S*)-**1**: δ_H(400 MHz, C_6D_6) 0.97 (d, *J* 6.8, 3H, CH_3), 1.13 (d, *J* 6.4, 3H, CH_3), 1.14 (q, *J* 12.4, 1H, $H5_{ax}$), 1.18 (s, 3H, CH_3), 1.25 (m, 1H, H3), 1.50 (s, 3H, CH_3), 1.71 (ddd, *J* 12.4, 4.8, 2.4, 1H, $H5_{eq}$), 1.92 (dd, *J* 13.2, 7.6, 1H, $H13_a$), 2.05 (m, 5H, $H13_b$, H16, H17), 2.18 (ddd, *J* 14.0, 7.2, 6.8, 1H, $H7_a$), 2.34 (ddd, 14.0, 7.2, 6.8, 1H, $H7_b$), 3.58 (dt, *J* 10.4, 4.4, 1H, H4), 3.84 (m, 1H, H6), 5.00 (d, *J* 10.4, 1H, H19), 5.05 (dd, *J* 17.2, 1.6, 1H, H19), 5.17 (br t, *J* 6.4, 1H, H15), 5.54 (dd, *J* 14.4, 7.6, 1H, H11), 5.70 (dt, 14. 7.2, 1H, H8), 5.79 (m, 1H, H18), 6.10 (m, 1H, H10), 6.13 (m, 1H, H9); δ_C (100 MHz, C_6D_6) 12.3 (C20), 16.1 (C22), 20.1 (C21), 27.8 (C16), 28.2 (C1), 34.4 (C17), 34.9 (C12), 39.7 (C7), 41.3 (C5), 47.2 (C3), 47.9 (C13), 68.3 (C6), 69.7 (C4), 98.9 (C2), 114.8 (C19), 126.2 (C15), 128.4 (C8), 128.8 (C10), 133.2 (C9), 133.8 (C14), 138.75 (C11), 138.81 (C18).

1 K. L. Erickson, J. A. Beutler, J. H. Cardellina II and M. R. Boyd, *Tetrahedron*, 1995, **51**, 11953.
2 C. M. Cerda-García-Rojas and D. J. Faulkner, *Tetrahedron*, 1995, **51**, 1087.
3 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508.
4 V. Farina, V. Krishnamurthy and W. J. Scott, in *Organic Reactions*, ed. L. A. Paquette, Wiley, New York, 1997, pp. 1–652.
5 H. C. Brown and K. S. Bhat, *J. Am. Chem. Soc.*, 1986, **108**, 293.
6 J. W. Burton, J. S. Clark, S. Derrer, T. C. Stork, J. G. Bendall and A. B. Holmes, *J. Am. Chem. Soc.*, 1997, **119**, 7483.
7 J. Tsuji, *Synthesis*, 1984, 369.
8 A. J. Leusink and H. A. Budding, *J. Organomet. Chem.*, 1968, **11**, 533.
9 M. Nishizawa and R. Noyori, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2233.
10 R. E. Ireland and R. H. Meuller, *J. Am. Chem. Soc.*, 1972, **94**, 5897.
11 E. J. Corey and A. Tramontano, *J. Am. Chem. Soc.*, 1984, **106**, 462.
12 F. Yasuhara, S. Yamaguchi, R. Kasai and O. Tanaka, *Tetrahedron Lett.*, 1986, **27**, 4033.
13 F. D. Riccardis, L. Minale, R. Riccio, B. Giovannitti, M. Iorizzi and C. Debitus, *Gazz. Chim. Ital.*, 1993, **123**, 79.
14 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277.
15 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.

Communication 9/04379I