Pergamon

Tetrahedron Letters 43 (2002) 1109–1111

TETRAHEDRON LETTERS

First enantiospecific synthesis of (–)-9-pupukeanone†

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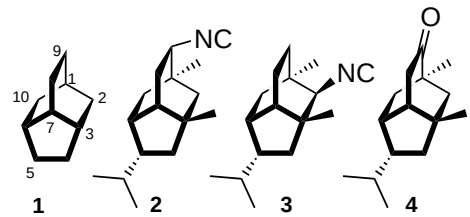
Received 11 October 2001; revised 26 November 2001; accepted 6 December 2001

Abstract—The first enantiospecific total synthesis of (–)-9-pupukeanone, starting from (*R*)-carvone employing a combination of Michael–Michael reaction and an intramolecular rhodium carbenoid C–H insertion reaction as key steps, is described.

The nudibranch *Phyllidia varicosa* Lamarck, 1801 secretes, as part of its defence mechanism, two volatile substances, which are lethal to fish and crustaceans. Scheuer and co-workers reported the isolation of these two isotwistane (**1**) based sesquiterpenes, 9- and 2-isocyanopupukeananes **2** and **3** from the skin extracts of *P. varicosa* and also from its prey, a sponge *Ciocalypta* sp., and the structures were elucidated based on degradative and single crystal X-ray diffraction studies.[1] The absolute stereochemistry was assigned based on the CD spectrum of 9-pupukeanone (–)-**4** obtained from the isonitrile **2**. The presence of an interesting isotwistane carbon framework made pupukeananes interesting and challenging synthetic targets. In 1979, the research groups of Corey[2a] and Yamamoto[2b] simultaneously reported the synthesis of (±)-9-isocyanopupukeanane **2** via 9-pupukeanone **4**. Almost at the same time White and Schiehser[2c] achieved the synthesis of (±)-**4**. Subsequently, the research groups of Piers[2d] and Chang[2e] reported the formal synthesis of (±)-**2**. However, so far, there is no report on the synthesis of either 9-isocyanopupukeanane or 9-pupukeanone in optically active form.[3] In continuation of our interest in the enantiospecific synthesis of sesquiterpenes containing the isotwistane carbon framework,[3,4] herein we report the first enantiospecific total synthesis of (–)-9-pupukeanone **4** starting from the readily available monoterpene, (*R*)-carvone, employing a rhodium carbenoid C–H insertion reaction as the key step.



We speculated that intramolecular rhodium carbenoid C–H insertion[5] of the diazo ketone derived from the carboxylic acid **5**, could generate the isotwistane **6**, an intermediate used in Yamamoto's synthesis of racemic 9-isocyanopupukeanane via 9-pupukeanone. Identifying the isopropenyl group as a masked hydroxy group, a strategy was conceived in which the Michael–Michael adduct **7** of appropriately substituted (*R*)-carvone and methyl acrylate[6] could serve as the starting material for the generation of carboxylic acid **5** via deoxygenation of the ketone group and degradation of the isopropenyl group (Scheme 1).

The synthetic sequence starting from 6-methylcarvone **9** is depicted in Scheme 2. Michael–Michael reaction of 6-methylcarvone **9** with lithium hexamethyldisilazide and one equivalent of methyl acrylate in hexane furnished the bicyclic keto-ester **7**.[6] As the double bond in **7** was found to isomerise on treatment with acid, degradation of the isopropenyl group was initially addressed. Thus, ozonolysis of the isopropenyl group in the keto-ester **7**, in a mixture of methylene chloride and methanol, followed by treatment of the resultant methoxy-hydroperoxide with acetic anhydride and triethylamine in refluxing benzene furnished the Criegee rearrangement[7] product **10** in 55% yield along with a varying amount (10–20%) of the normal ozonolysis product **11**. Reaction of the keto-ester **10** with ethanedithiol in benzene in the presence of boron tri-

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† Chiral synthons from carvone, Part 53. For Parts 51 and 52, see Ref. 8.

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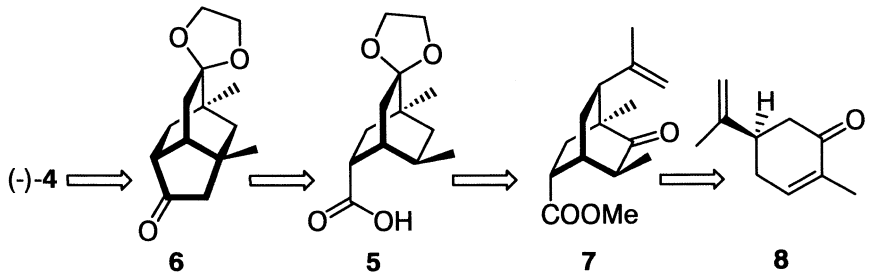
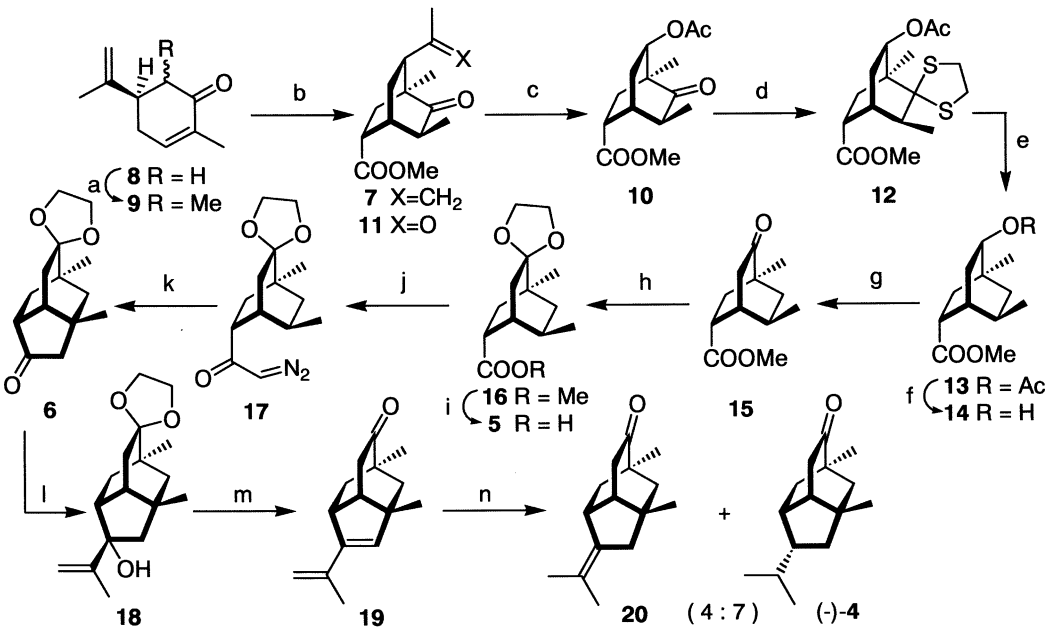


Scheme 1.

fluoride etherate furnished the thioketal **12**, which on desulfurisation with Raney nickel in refluxing ethanol generated the key intermediate of the sequence, acetoxy-ester **13**, $[\alpha]_D^{24}=-128.5$ (*c* 3.4, $CHCl_3$). Hydrolysis of the acetate group in **13**, followed by oxidation of the resultant hydroxy-ester **14** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished the keto-ester **15**, $[\alpha]_D^{24}=-53$ (*c* 3.6, $CHCl_3$). To avoid regiochemical problems at a later stage, the ketone group in the keto-ester **15** was protected with ethanediol and *p*-toluenesulfonic acid (*p*-TSA) in refluxing benzene to furnish the ketal-ester[‡] **16**. Next, attention was turned towards the conversion of the ketal-ester **16** into the isotwistane **6**, an intermediate in the synthesis of racemic 9-pupukeanone by Yamamoto and Sham.[2b] Hydrolysis of the ester group in the ketal-ester **16** furnished the acid **5**, which was converted into the diazo ketone **17** via the corresponding acid chloride. Treatment of the diazo ketone **17** with a catalytic amount of rhodium trifluoroacetate in refluxing methylene chloride furnished the isotwistane[‡] **6** in a regiospecific manner, which exhibited ^1H and ^{13}C NMR spectral data identical to that of the racemic compound.[2b,e] The keto-ketal **6** was then transformed[2b] into 9-pupu-



Scheme 2. *Reagents, conditions and yields*: (a) LDA, THF, MeI, 0°C→rt, 10 h, 98%; (b) LiHMDS, hexane, CH_2=CHCOOMe, 0°C→rt, 3 h, 70%; (c) i. O_3/O_2, CH_2Cl_2–MeOH (5:1), −70°C; ii. Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 5 h; 55%; (d) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, C_6H_6, 20 h, 68%; (e) Raney Ni, EtOH, reflux, 6 h, 94%; (f) K_2CO_3, MeOH, rt, 3 h, 91%; (g) PCC, silica gel, CH_2Cl_2, rt, 2 h, 90%; (h) $(CH_2OH)_2$, *p*-TSA, C_6H_6, reflux (Dean–Stark), 85%; (i) 5% NaOH, H_2O–MeOH (1:1), reflux, 8 h, 90%; (j) i. $(COCl)_2$, C_6H_6, py, rt, 2 h; ii. CH_2N_2, Et_2O, 0°C→rt, 2 h; (k) $Rh_2(tfa)_4$, CH_2Cl_2, reflux, 3 h; 57% (from the acid **5**); (l) CH_2=C(Me)Li, Et_2O, −70°C, 1 h, 71%; (m) *p*-TSA, CH_2Cl_2, rt, 4 h, 90%; (n) PtO_2, H_2, MeOH, rt, 24 h, 90%.

‡ All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the ketal-ester **16**: $[\alpha]_D^{24}=-80.2$ (*c* 4.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1734. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.00–3.70 (4 H, m), 3.67 (3 H, s), 2.65 (1 H, br t, $J=9$ Hz), 1.96 (1 H, dd, $J=14.4$ and 2.2 Hz), 1.90–1.50 (5 H, m), 1.46 (1 H, dd, $J=13.4$ and 10 Hz), 1.20 (1 H, ddd, $J=13.5$, 7.5 and 3 Hz), 0.93 (3 H, d, $J=6.9$ Hz), 0.78 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 175.5 (C), 111.6 (C), 64.9 (CH_2), 64.4 (CH_2), 51.6 (CH_3), 42.2 (CH), 38.3 (CH_2), 37.4 (CH_2), 36.6 (C), 36.5 (CH), 31.1 (CH_2), 25.9 (CH), 20.1 (CH_3), 19.7 (CH_3). For the isotwistane **6**: $[\alpha]_D^{25}=+49$ (*c* 2.1, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1742. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.00–3.70 (4 H, m), 2.31 (1 H, dd, $J=11.2$ and 4.5 Hz), 2.30–1.80 (7 H, m), 1.30–1.15 (2 H, m), 1.19 (3 H, s), 0.75 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 220.2 (C), 110.0 (C), 64.95 (CH_2), 64.93 (CH_2), 55.9 (CH_2), 47.6 (CH), 45.3 (CH_2), 42.2 (CH), 37.3 (C), 36.7 (C), 33.9 (CH_2), 33.0 (CH_2), 25.3 (CH_3), 19.4 (CH_3).

keanone **4**. Thus, addition of isopropenyllithium to the keto-ketal **6** generated the allyl alcohol **18**, which on treatment with *p*-TSA in methylene chloride directly furnished the dienone **19**, $[\alpha]_D^{26} = -40$ (*c* 1.9, $CHCl_3$), via simultaneous dehydration and hydrolysis of the ketal moiety. Finally, hydrogenation of the dienone **19** in methanol with platinum oxide as the catalyst followed by purification on a silver nitrate impregnated silica gel column furnished[2c] the enone **20**, $[\alpha]_D^{25} = -51$ (*c* 1.7, $CHCl_3$), and 9-pupukeanone (−)-**4**, $[\alpha]_D^{26} = -42.5$ (*c* 0.7, CCl_4) [lit.[1a] $[\alpha]_D = -48$ (*c* 0.54, CCl_4)]. The synthetic 9-pupukeanone (−)-**4** was found to be identical to the compound derived from the natural product 9-isocyanopupukeanane.

In conclusion, we have accomplished the first enantiospecific total synthesis of (−)-9-pupukeanone employing an intramolecular rhodium carbenoid C–H insertion reaction as the key step. The present sequence also confirms the absolute stereochemistry[1b] of pupukeananes.

Acknowledgements

We thank Professor J. D. White for providing the copies of the IR and ^{1}H NMR spectra of a mixture of the isotwistanones **20** and **4**; and the Council of Scientific and Industrial Research, New Delhi for the award of a research fellowship to P.R.K.

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