Syntheses of Enantiomerically Pure *ent*-Multifidene and Related Compounds

Peter Kramp,[a] Günter Helmchen*[a] and Andrew B. Holmes[b]

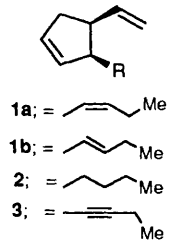
[a] *Organisch-chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-6900 Heidelberg, Germany*
[b] *University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW*

Enantiomers of multifidene and related compounds were synthesized from (1*R*)-7-*syn*-carboxy-2-norbornanone *via* Norrish Type I cleavage.

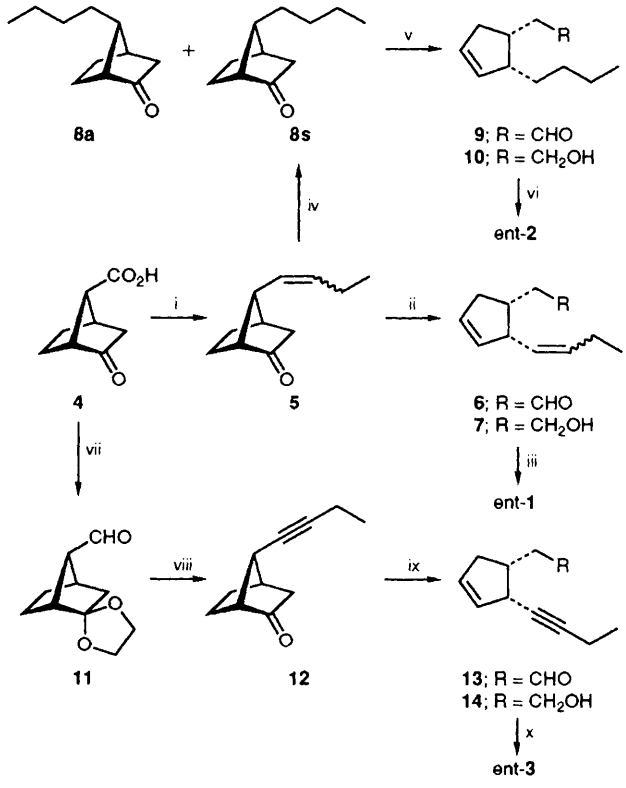
Multifidene **1a** and the more saturated derivative **2** were isolated[1a] from brown algae. Much interest has been focused on **1a** because of its intriguing biological activity.[1b] Only minute amounts are available by isolation and, therefore, syntheses of the enantiomerically pure compounds (EPCs) are required for biological tests. In order to assist structure–activity studies we have prepared enantiomers of the natural products *via* routes equally applicable to the latter. In addition, we have prepared the dehydro derivative *ent*-**3** of potential interest in this connection. High biological activity of **1a** demands a high level of enantiomeric purity for *ent*-**1a** in order to draw reliable conclusions from biotests. Previously, several syntheses of racemic and enantiomerically impure compounds were reported.[2a–f] To the best of our knowledge, only one EPC synthesis has so far been accomplished.[2g]

Our starting material was (+)-(1*R*,4*R*,7*S*)-7-*syn*-carboxy-norbornanone **4**,† which is available on a multigram scale *via* asymmetric Diels–Alder reaction.[3] This compound allows preparation of *cis*-1,2-disubstituted cyclopentanes *via* functional group manipulation and appropriate opening of the 1,2-bond,[4] here by a Norrish Type I process,[5] which generates the endocyclic double bond and the C_2-chain of *ent*-**1**–*ent*-**3**.

The route towards *ent*-**1a** commenced with a Rosenmund reaction of (+)-**4** followed by a Wittig reaction to give a 97 : 3 mixture of (*Z*)-**5** and (*E*)-**5**. The crucial photolysis‡ proceeded smoothly, but with concomitant *Z*–*E* isomerization to give aldehydes **6** which were reduced *in situ* to a 3 : 1 mixture of the alcohols (*Z*)-**7** and (*E*)-**7** (Scheme 1); among a variety of *O*-acyl derivatives none was found that allowed separation of the *Z*/*E*-isomers. Consequently, elimination by Gilman *et al.*'s method[6] was carried out to give a 3 : 1 mixture of *Z*- and *E*-*ent*-multifidenes **1a,b** which were separated by preparative GLC.§ The chemical and enantiomeric purity of *ent*-**1a** was >99% according to GLC on a cyclodextrin phase;¶ the optical rotation of $[\alpha]_{578}^{20}$ −272.5 (*c* 0.86, CCl_4) was in excellent agreement with the value $[\alpha]_{578}^{20}$ −271.0 (*c* 0.428, CCl_4; >97% enantiomeric excess) previously reported by Boland *et al.*[2g]



In order to avoid *Z*–*E* isomerization, a route to the alkyne *ent*-**3**, which can be cleanly reduced to *ent*-**1a** as previously demonstrated,[2f] was developed. The intermediate **12** was obtained *via* the keto protected aldehyde **11** *via* a standard protocol.[7] Photolysis proceeded in essentially quantitative yield (GC–MS), but isolation of the alcohol **14** furnished only a 54% yield owing to great sensitivity of this compound. Elimination as above gave *ent*-**3** with optical rotation of $[\alpha]_D^{20}$ −353.5 (*c* 1.19, $CHCl_3$).



Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, benzene, room temp., then $Pd/BaSO_4$, *N*,*N*-dimethylaniline, H_2, benzene, room temp., then $PrPPh_3Br$, $(Me_3Si)_2NNa$, THF, −78 °C (30 min) to room temp., 69% [(*Z*)-**5** : (*E*)-**5** = 97 : 3]; ii, *hν* (300 nm), MeOH, room temp., then $NaBH_4$, MeOH, 0 °C, 79% [(*Z*)-**7** : (*E*)-**7** = 3 : 1]; iii, *o*-$NO_2C_6H_4SeCN$, Bu^n_3P, THF, room temp., then H_2O_2, THF, room temp., 76% (*ent*-**1a** : *ent*-**1b** = 3 : 1); iv, Pd/C, H_2, EtOH, room temp., 92% (**8s** : **8a** = 83 : 17); v, *hν* (300 nm), MeOH, 0 °C, then $NaBH_4$, MeOH, 0 °C, 58%; vi, *o*-$NO_2C_6H_4SeCN$, Bu^n_3P, THF, room temp., then H_2O_2, THF, room temp., 80%; vii, CH_2N_2, Et_2O, room temp., then *p*-$MeC_6H_4SO_3H{\cdot}H_2O$, $HOCH_2CH_2OH$, benzene, reflux, 94%, then $LiAlH_4$, Et_2O, room temp., then DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C, 90%; viii, PPh_3 (4 equiv.), CBr_4 (2 equiv.), CH_2Cl_2, 0 °C, then Bu^nLi (3 equiv.), −65 °C (1.5 h), room temp. (30 min), then EtI (4 equiv.), HMPT, −60 °C (15 min) to room temp., then 1 mol dm^{-3} HCl–THF (1 : 1), room temp., 74%; ix, *hν* (300 nm), MeOH, room temp., then $NaBH_4$, MeOH, 0 °C, 54%; x, *o*-$NO_2C_6H_4SeCN$, Bu^n_3P, THF, room temp., then H_2O_2, THF, room temp., 50%; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; HMPT = hexamethylphosphoric triamide

† Satisfactory analytical (combustion and/or high resolution mass) and spectral (^1H NMR, ^{13}C NMR, mass) data were obtained for all new compounds.

‡ Medium-pressure mercury lamp Hannovia TQ 150.

§ *Separation conditions*: Varian Aerograph, model 920 (WLD steel column 2 m × 4 mm, 20% fraktonitrile III on Chromosorb P 60–80 mesh (acid washed, treated with dimethylchlorosilane); carrier gas H_2, flow 40 ml min^{-1}, column temp. 65 °C. We thank Professor W. Boland, Karlsruhe, for generous help in the GLC separation of *ent*-**1a** and *ent*-**1b**.

¶ WCOT (wall coated open tubular) fused silica, CP-cyclodextrin-β-2,3,6-M-19 (Chrompac), 50 m, film thickness 0.25 μm, 0.25 mm internal diameter.

Finally, the enantiomer *ent*-**2** of the more saturated natural compound **2** was prepared from **5**. Catalytic hydrogenation of **5** gave a 83 : 17 mixture of the C-7 epimers **8s** and **8a** which were easily separated by MPLC. Photolysis, reduction and elimination in the way described above furnished *ent*-**2** with optical rotation of $[\alpha]_D^{20}$ −180.3 (*c* 2.0, CH_2Cl_2), in excellent agreement with a previously reported value of $[\alpha]_D^{20}$ −162.7 (*c* 5.27, CH_2Cl_2)[8] for material of 90.2% enantiomeric purity.

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