# Total Synthesis of Naturally Occurring Granaticin

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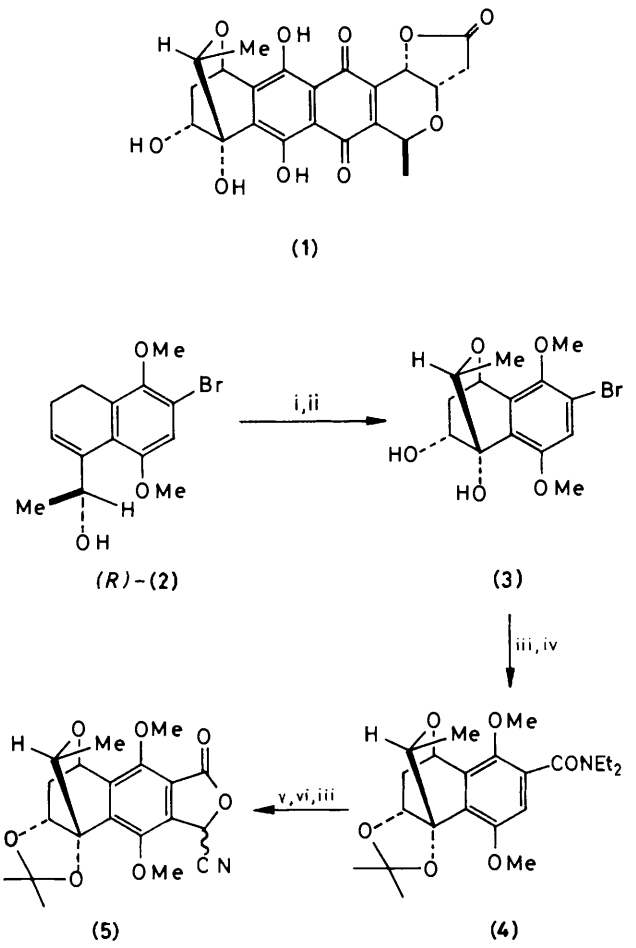
Natural granaticin (**1**) has been synthesized by joining the chiral left and right fragments, (**5**) and (**10**), and subsequent lactonization of the resulting product (**11**) and oxidative *O*-demethylation.

Granaticin (**1**)[1] is a structurally unique member of the pyranonaphthoquinone antibiotics, and its synthesis has been the subject of considerable interest. Recently we reported the first total synthesis of (**1**) in racemic form.[2] We now describe a stereocontrolled synthesis of optically active natural granaticin, which, in a key step, employs benzannulation between the pentacyclic phthalide (**5**) and dihydropyranone (**10**), both having the correct absolute stereochemistry.

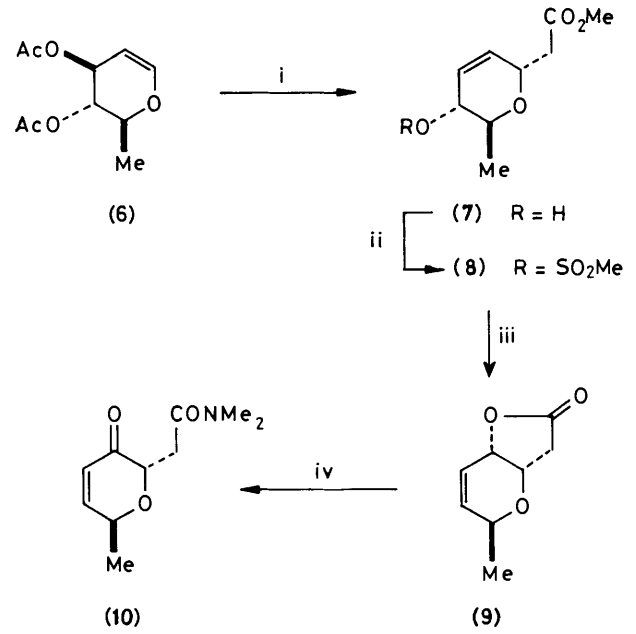


**Scheme 1.** *Reagents and conditions*: i, $OsO_4$, $Me_3N(O)$, $Bu^tOH$–$H_2O$, 4 h; ii, *N*-bromosuccinimide, azoisobutyronitrile, $CCl_4$, 40 °C, 30 min, then $AgClO_4$, tetrahydrofuran (THF), room temp., 10 min; iii, excess of 2-methoxypropene, THF, camphorsulphonic acid, room temp., 1 h; iv, $Bu^nLi$ (1.1 equiv.), THF, −100 °C, 3 min, then $Et_2NCOCl$ (2.8 equiv.), −70 °C to room temp., 1.5 h; v, $Bu^tLi$ (3 equiv.), THF, −78 °C, 1 h, then dimethylformamide (4.3 equiv.), 0 °C, 15 min; vi, $Me_3SiCN$, $CH_2Cl_2$, catalytic amount of 18-crown-6–KCN complex, 0 °C, 15 min, then AcOH, room temp., 24 h.

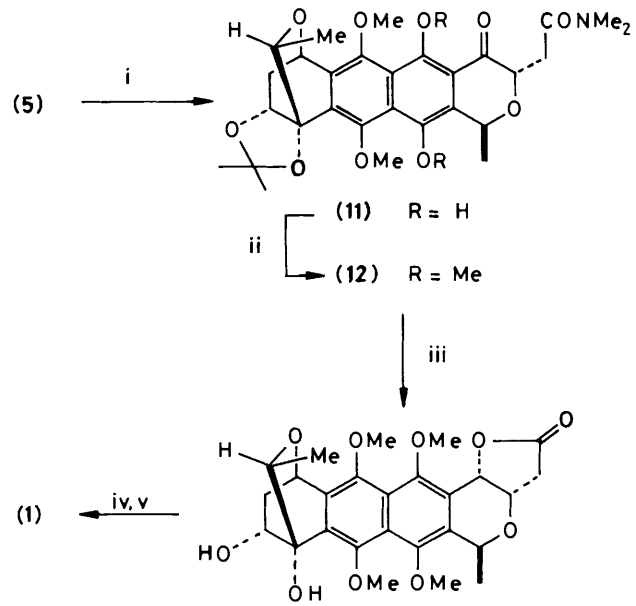
The optically active starting material (*R*)-(**2**)† leading to (**5**) was first converted into compound (**3**), m.p. 153—55 °C, $[\alpha]_D^{25}$ +52.2° (*c* 1.53, $CHCl_3$), according to the procedure reported for the racemate;[3] highly diastereoselective catalytic osmylation followed by *N*-bromosuccinimide-mediated cyclization (46% overall yield) (Scheme 1). The bromine substituent in (**3**) was then replaced by the *N*,*N*-diethylcarbamoyl group by sequential treatment of its acetonide with n-butyllithium and $Et_2NCOCl$ to give (**4**) in 74% yield. Transformation of benzamide (**4**) into cyanophthalide (**5**)‡ was carried out by our improved procedure[4] (32% overall yield).

† This enantiomer, $[\alpha]_D^{25}$ +12.4° (*c* 0.67, $CHCl_3$), was obtained by resolution of (±)-(**2**) in high yield *via* the (−)-*N*-(1-phenylethyl)carbamate, and the absolute configuration was determined by the exciton chirality method as applied to the *O*-benzoate of the corresponding naphthyl carbinol (K. Okazaki, Dissertation for Doctor's degree, March 1988). For the preparation of (±)-(**2**), see ref. 3.

‡ For the synthesis of regioisomeric cyanophthalide (racemic), see ref. 2.



**Scheme 2.** *Reagents and conditions*: i, $CH_2$=C(OMe)$OSiMe_2Bu^t$ (1.25 equiv.), $BF_3$–ether (1.5 equiv.), toluene, −78 °C, 1.5 h, then 1% KOH–MeOH, room temp., 10 min; ii, $MeSO_2Cl$ (2.5 equiv.), $Et_3N$ (8 equiv.), $CH_2Cl_2$, 0 °C to room temp.; iii, silica gel chromatography (hexane–AcOEt, 2 : 1); iv, $Me_2AlNMe_2$ (1.3 equiv.), $CH_2Cl_2$, 0 °C to room temp., 1.5 h, then pyridinium chlorochromate, AcONa, molecular sieves 3Å, $CH_2Cl_2$, −10 °C, 40 min.



**Scheme 3.** *Reagents and conditions*: i, $MeSOCH_2Li$ (3.4 equiv.), $Bu^tOH$ (3.1 equiv.), tetrahydrofuran (THF), −78 °C, 15 min, then (**10**), −78 °C to room temp., 14 h; ii, $Me_2SO_4$ (8 equiv.), $K_2CO_3$ (17 equiv.), acetone, reflux, 40 min; iii, $LiBBu^s_3H$ (2 equiv.), THF, −78 °C, 1 h, then $Me_3SiCl$ (6 equiv.), THF, room temp., 23 h; iv, excess of 2-methoxypropene, camphorsulphonic acid, THF, room temp.; v, cerium(IV) ammonium nitrate, MeCN, then $AlCl_3$ (6 equiv.), $Et_2S$ (24 equiv.), $CH_2Cl_2$, room temp.

Preparation of the Michael acceptor (**10**) starting from di-*O*-acetylrhamnal (**6**) (Scheme 2) was commenced by reaction of (**6**) with ketene methyl t-butyldimethylsilyl acetal in the presence of $BF_3$–$Et_2O$ in toluene at low temperature.[5]

The *C*-glycosides, (**7**) and the C-1 epimer (3:2 ratio, 64% yield), were obtained after *O*-deacetylation and chromatographic separation. The *O*-methanesulphonate (**8**) of (**7**) readily underwent an intramolecular $S_N2'$ reaction on silica gel chromatography to afford the γ-lactone (**9**)§ [87% yield from (**7**)], m.p. 88—91 °C, $[\alpha]_D^{25}$ +185° (*c* 0.805, $CHCl_3$). The lactone (**9**) was then converted to the γ-keto carboxamide (**10**) by aminolysis with $Me_2AlNM_2$[6] followed by oxidation with pyridinium chlorochromate[7] (82% yield).

Coupling of the chiral fragments (**5**) and (**10**) was carried out in the presence of $LiCH_2SOMe$ (excess)[2] affording the hexacyclic naphthalene-1,4-diol derivative (**11**) in *ca.* 50% yield, which on *O*-methylation gave (**12**) (Scheme 3). The ketone carbonyl group in (**12**) was then reduced with lithium tri-s-butylborohydride to produce the *cis*-γ-hydroxycarboxamide predominantly, which could be easily lactonized by treatment with chlorotrimethylsilane in wet $CH_2Cl_2$[8] to afford (**13**) (56% overall yield), $[\alpha]_D^{25}$ −158° (*c* 0.203, $CHCl_3$).

Finally, oxidative *O*-demethylation of (**13**) according to the same method as applied to racemate[2] afforded (**1**) in 62% yield from (**13**) after chromatographic purification. The synthetic granaticin [deep red crystals from AcOEt, m.p. and mixed m.p. 211—213 °C (decomp.)] proved to be identical chromatographically and spectroscopically ($^1H$ n.m.r., i.r., u.v., and c.d.¶) with an authentic sample of natural granaticin provided by Dr. H. H. Peter, Ciba-Geigy Ltd., Switzerland.

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§ The stereochemistry was determined by differential nuclear Overhauser enhancement performed with (**9**) and the diastereoisomeric *cis*-lactone derived from the C-1 epimer of (**7**). $^1H$ N.m.r. data for (**9**) (270 MHz, $CDCl_3$): δ 1.30 (d, *J* 6.8 Hz, 3H), 2.60 (d, *J* 17.3 Hz, 1H), 2.82 (dd, *J* 17.8, 5.1 Hz, 1H), 4.40 (qdd, *J* 6.8, 3.7, 2.0 Hz, 1H), 4.55 (m, 2H), 6.00 (ddd, *J* 10.3, 4.2, 2.0 Hz, 1H), 6.21 (dd, 10.3, 3.7 Hz, 1H).

¶ C.d. data of (**1**) [λ/nm (Δε) in EtOH]: 202 (+5.52), 221 (−5.70), 230 (+0.35), 240 (−1.55), 258 (+0.17), 276 (−0.52), 310 (+1.73), 386 (−1.73), 430 (−1.03), 526 (−2.42).

## References

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