234. Novel Variant of the Tricyclooctanone Approach to Cyclopentanoid Natural Products

Synthesis of (±)-Coriolin

Preliminary Communication

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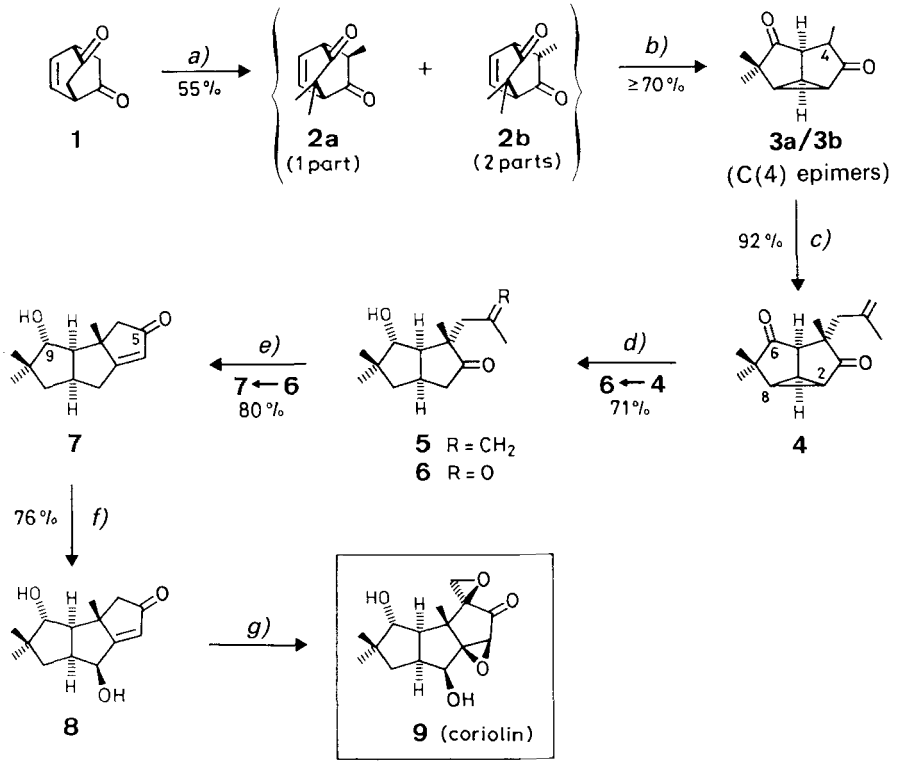
Summary

A total synthesis of the antitumor sesquiterpene coriolin (**9**; racemic) in 11 steps from 3,3,6-trimethylbicyclo[2.2.2]oct-7-ene-2,5-dione (**2a**/**2b**) is described (yield **2a**/**2b**→**8**: 28%). The sequence is unprecedentedly short and avoids difficult separation problems. The key step in the scheme is a novel facet of oxadi-π-methane photochemistry, *i.e.*, the steering by subtle steric effects of the β,γ-unsaturated ε-diketone to undergo a regioselective photorearrangement involving one β,γ-enone partial chromophore. Furthermore, the overall phototransformation, which can be carried out at unusually high concentrations ($\geq 20\%$ solutions), involves also a *Norrish* type I process equilibrating the two epimeric starting enediones **2a** and **2b** in favour of the desired stereoisomer.

The antitumor sesquiterpene coriolin, (−)-(**9**)[1]), has become a testing case for the design of syntheses of medium-sized natural products of complex structures, and notably for the development of new methodologies aiming at cyclopentanoid annulation procedures [4]. We have previously demonstrated that the use of the optically active forms of tricyclo[3.3.0.$0^{2,8}$]octan-3-one provides for a versatile synthetic approach to cyclopentanoid natural products [3] [5] [6], including one towards the total synthesis of coriolin, (−)-(**9**) [6]. *Scheme 1* summarizes an alternative to this concept which is characterized by an unprecedentedly short route to the intermediate **8** in common with previous total syntheses of (±)-coriolin (**9**) [2]. The key step in this scheme is a novel facet of oxadi-π-methane photochemistry, *i.e.*, the steering by subtle steric effects of a β,γ-unsaturated ε-diketone to undergo a regioselective photorearrangement involving one β,γ-enone partial chromophore.

[1]) Synthetic work directed towards (±)-**9**, see [1]; synthesis of **8** and its conversion into (±)-**9**, see [2]. For the isolation of (−)-**9** and its biological importance, see *Footnote 82* in [3].

Scheme 1. *Synthesis of (±)-Coriolin*[2])



a) NaH (2 equiv.), dimethoxyethane, + 80°C, 30 min; NaH (1 equiv.), 18-crown-6 ether, MeI, r.t. *b*) ≥ 20% Acetone or hexane solutions, *hν* (λ(irr.) 300 nm), r.t. *c*) Methylallyl chloride, KBr, *t*-BuOK, *t*-BuOH, toluene, + 50°C, 1 h. *d*) Li, NH_3, EtOH, − 78°C, 5 min; OsO_4, $NaIO_4$, THF/H_2O, r.t. *e*) KOH, MeOH, r.t. *f*) Isopropenyl acetate, TsOH, reflux; oxone (= $2KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$), $NaHCO_3$, THF/H_2O, r.t. *g*) [2a].

Bicyclo[2.2.2]oct-7-ene-2,5-dione (**1**) is prepared from hydroquinone and maleic anhydride[3]). The three CH_3-groups were introduced in a one-pot operation: a solution of **1** in dimethoxyethane was first treated with 2 equiv. of NaH at 80°C. The solution was then cooled to room temperature, and an excess of MeI was added followed by the successive addition of a third equiv. of NaH, of crown ether, and of another portion of MeI. The judiciously chosen conditions minimized the formation of tetramethylated diketone, and a 1:2 mixture of the trimethyl epimers **2a** and **2b** was obtained in 55% yield[4])[5a]). Both solvent-sensitized (acetone) and direct (hexane) irradiation of **2a**/**2b** with λ(irr.) 300 nm [9] afforded the photoproducts **3a**/**3b**[5a]) (≥ 70% yield) and **10a**,**b** *(Scheme 2)*. Highest yields of **3a**/**3b** were obtained with unusually concentrated solu-

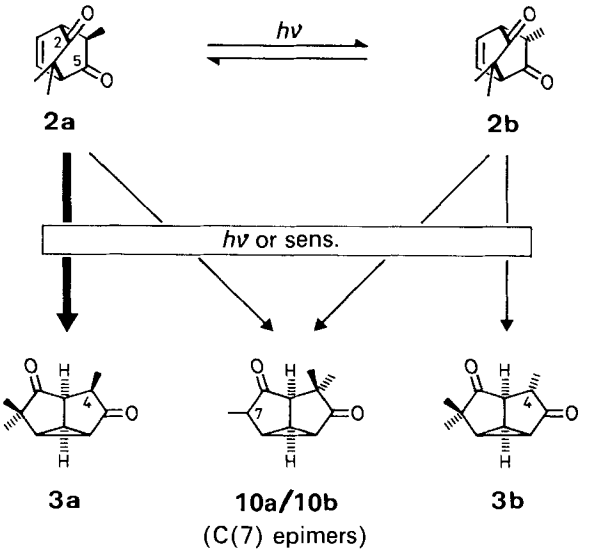
[2]) The formulae of all compounds except coriolin stand for *racemic* materials.

[3]) The overall yield of **1** from hydroquinone and maleic anhydride has been improved by *Weitemeyer & de Meijere* [8a] compared with that initially reported [7]. For experimental details, see [8b].

[4]) Yields refer to isolated and purified products (column chromotography on either silica gel or *Florisil*).

[5]) a) Satisfactory spectral data (270-MHz ^{1}H-NMR, IR, and MS) were obtained. b) Correct combustion analytical data for the C,H elemental composition were obtained.

Scheme 2. *Photochemical Channels Leading to* **3a** *and* **3b** *in* $\geq 70\%$ *Yield*[2])



tions ($\geq 20\%$) and even with neat **2a**/**2b**. The product mixture could be used directly in the subsequent alkylation, in which **3a**/**3b** yielded the single product **4**[6]), and **10a**/**10b** were decomposed under the alkaline conditions. For the alkylation (of **3a**/**3b**) and the oxidative cleavage (of **5**) to **6**[5])[6])[7]), conditions described earlier [6] for related transformations were applied. The intervening *Birch* reduction **4**→**5**[5a]) was highly selective with respect to both the regiochemistry of the cyclopropane cleavage (opening between C(2) and C(8)) and the stereochemistry of the C(6) ketone reduction to the thermodynamically favored *'exo'* hydroxyl group[8]).

For the base-catalyzed ring closure **6**→**7**[5a]), known procedures [1] [2] previously applied in related work [6] were adopted. The sequence was completed by treatment of the dienol acetate derivative of **7** with oxone [11] to give a product which was identified with an authentic sample of **8** [2a] by mixed melting point and comparison of the chromatographic behavior (TLC, GLC) and spectral data (UV, IR, 270-MHz ^{1}H-NMR). This compound has already been converted further into (±)-coriolin [2a].

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[6]) Spectral key data of **4**: ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 0.89, 1.0, 1.24, 1.77 (4 *s*, each 3H); 1.8–2.35 (*m*, 4H); 2.72 (*dd*, J = 5, 10, 1H); 2.96 (*d*, J = 4.5, 1H); 4.75, 4.96 (2 *m*, each 1H). ^{13}C-NMR ($CDCl_3$, 20.1 MHz): δ 39.5, 58.8, 128.3, 215.1, 220.2, (5 *s*); 18.5, 22.4, 46.2, 56.6 (4 *d*); 48.4, 116.6 (2 *t*); 24.4, 26.5, 26.8, 35.6 (4 *q*). IR ($CHCl_3$): 1735, 1715 cm^{-1}. MS: *m*/*z* 232 (M^+, $C_{15}H_{20}O_2$), 217, 162, 149, 121, 91, 55, 41 (base peak). **6**: ^{1}H-NMR ($CDCl_3$, 270 MHz): δ 0.90, 1.03, 1.12, 2.10 (4 *s*, each 3H); 1.54 (*s*, 1H); 1.9–2.15 (*m*, 3H); 2.36 (*t*, J = 10, 1H); 2.5 (1H, exchangeable with D_2O); 2.58 (*d*, J = 10, 1H); 2.70, 2.91 (2 *d*, each J = 18, 1H); 3.69 (*d*, J = 5, 1H). IR ($CHCl_3$): 3590, 3500, 1720, 1710 cm^{-1}. MS: *m*/*z* 220 (M^+, $C_{14}H_{22}O_3$–H_2O), 177, 162, 135, 109, 55, 43 (base peak).

[7]) For the purpose of the synthetic sequence, purification was not required at this stage; for spectroscopic analysis, a sample of the product was chromatographed on silica gel.

[8]) The formation of any regio- and stereoisomers of **5** was below the ^{1}H-NMR detection limit of $< 2\%$. The configuration at C(9) follows from the conversion into the known [2a] product **8**. See [10] for a precedent of the regioselective reductive cleavage of the external cyclopropane bond in tricyclo[3.3.0.0^{2,8}]octan-3-one, and [1a] for precedents of the stereoselective reduction of the 6-keto group in a related system.

The overall yield of the new sequence **1**→**8** is 16%, and the total synthesis of (±)-coriolin *via* this route comprizes 12 steps, when the one-step final epoxidation procedure of *Danishefsky et al.* [1a] is followed.

The yield of the photoproducts **3a** and **3b** is remarkably high in view of the complexity of the chromophore of **2** and the heterogeneity of the starting material used. Two photoreactions are in fact operative in the transformation of **2a**/**2b**. A *Norrish* type I α-cleavage and thermal reclosure of the acyl-alkyl biradical [12][9]) rapidly interconverts the two epimers **2a** and **2b** *(Scheme 2)*. The initial 1:2 ratio obtained in the alkylation step (**1**→**2a** + **2b**) is thus equilibrated upon excitation at 300 nm in favor of **2a**[10]). Monitoring of the reaction by GLC showed that **2a** rearranges much faster than the epimer **2b** and that the rearrangement of **2a** preferentially forms product **3a** rather than the corresponding regioisomer **10**. We assign this favorable steering of the reaction to steric crowding in the photochemical bonding between the carbonyl C-atom and the olefinic β C-atom, exerted by the CH_3-groups (one in **2a** and two in **2b**) situated *cis* to the double-bond bridge. Such steric control can be attributed in each stereoisomer to one of the quaternary CH_3-groups and, additionally, in **2b** also to the secondary CH_3-group. The least hindered oxadi-π-methane channel is thus available to **2a**. It involves the C(5) keto group and specifically leads to **3a**, whereas the less efficient analogous rearrangement of **2b** affords **3b**. It should be noted that the two stereoisomers are synthetically of equal use.

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REFERENCES

[1] a) *S. Danishefsky, R. Zamboni, M. Kahn & S.J. Etheredge*, J. Am. Chem. Soc. *102*, 2097 (1980); *103*, 3460 (1981); *S. Danishefsky & R. Zamboni*, Tetrahedron Lett. *21*, 3439 (1980); b) *K. Tatsuta, K. Akimoto & M. Kimoshita*, J. Antibiot. *33*, 100 (1980); Tetrahedron *37*, 4365 (1981); c) *M. Shibasaki, K. Iseki & S. Ikegami*, Synth. Commun. *10*, 551 (1980); d) *M. Shibasaki, K. Iseki & S. Ikegami*, Tetrahedron Lett. *21*, 3587 (1980); *K. Iseki, M. Yamazaki, M. Shibasaki & S. Ikegami*, Tetrahedron *37*, 4411 (1981); e) *P.A. Wender & J.J. Howbert*, Tetrahedron Lett. *24*, 5325 (1983); f) *M. Koreeda & S.G. Mislankar*, J. Am. Chem. Soc. *105*, 7203 (1983).

[2] a) *B.M. Trost & D.P. Curran*, J. Am. Chem. Soc. *103*, 7380 (1981); b) *T. Ito, M. Tomiyoshi, K. Nakamura, S. Azuma, M. Izawa, F. Murayama, M. Yanagiva, H. Shirahama & T. Matsumoto*, Tetrahedron Lett. *23*, 1721 (1982); Tetrahedron *40*, 241 (1984); *G. Mehta, A.V. Reddy, A.N. Murthy & D.S. Reddy*, J. Chem. Soc., Chem. Commun. *1982*, 540; *C. Exon & P. Magnus*, J. Am. Chem. Soc. *105*, 2477 (1983).

[3] *M. Demuth & K. Schaffner*, Angew. Chem. *94*, 809 (1982); ibid. Int. Ed. *21*, 820 (1982).

[4] *L.A. Paquette*, Top. Curr. Chem. *119*, 1 (1984).

[5] *G. Mikhail & M. Demuth*, Helv. Chim. Acta *66*, 2362 (1983); *M. Demuth, S. Chandrasekhar & K. Schaffner*, J. Am. Chem. Soc. *106*, 1092 (1984); *P. Ritterskamp, M. Demuth & K. Schaffner*, J. Org. Chem. *49*, 1055 (1984).

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[9]) The formation of < 10% of cyclobutanone isomers – the alternative *Norrish* type I products by way of allylic 1,3-acyl shifts – was indicated by combined IR and GLC screening of the crude reaction mixture.

[10]) The photoequilibrium **2a**⇌**2b** typically is attained within a few minutes, whereas the full conversion of **2a**/**2b** to **3a**/**3b** and **10a**/**10b** requires an irradiation period of 3 h.

[6] *M. Demuth, A. Canovas, E. Weight, C. Krüger & Y.-H. Tsay,* Angew. Chem. *95,* 747 (1983); ibid. Int. Ed. *22,* 721 (1983); Angew. Chem. Suppl. *1983,* 1053.
[7] *C. A. Grob & A. Weiss,* Helv. Chim. Acta *43,* 1390 (1960).
[8] a) *C. Weitemeyer & A. de Meijere,* Angew. Chem. *88,* 721 (1976); ibid. Int. Ed. *15,* 686 (1976); b) *C. Weitemeyer,* Ph. D. Thesis, University of Hamburg, 1976.
[9] *M. Demuth, P. R. Raghavan, C. Carter, K. Nakano & K. Schaffner,* Helv. Chim. Acta *63,* 2434 (1980).
[10] *S. A. Monti, D. J. Bucheck & J. C. Shepard,* J. Org. Chem. *34,* 3080 (1969).
[11] *S. N. Suryawanshi & P. L. Fuchs,* Tetrahedron Lett. *22,* 4201 (1981).
[12] *H. Wehrli & K. Schaffner,* Helv. Chim. Acta *45,* 385 (1962).