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SYNTHESIS AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF THE MACRODIOLIDE (+)-CONGLOBATIN

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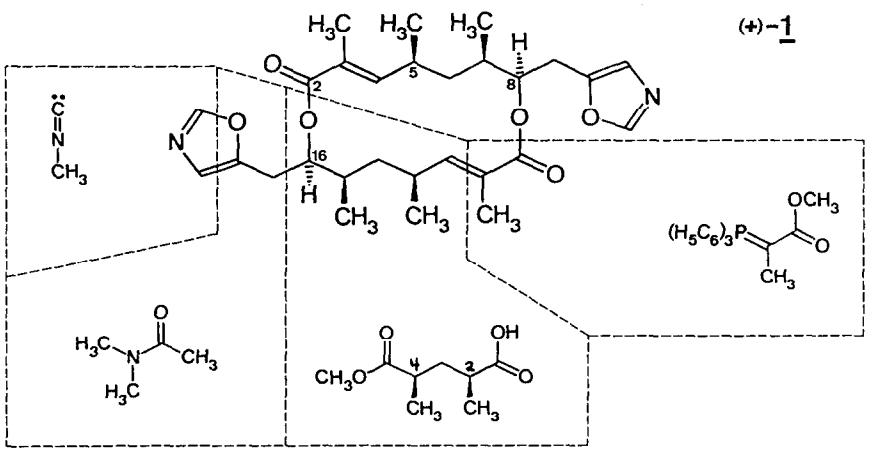
Summary: *(+)-Conglobatin is synthesized from (-)-(2S,4R)-2.4-dimethyl glutaric acid half-ester in 15 steps (total yield 4.4%). The synthesis proves the sense of chirality of the natural (-)-conglobatin to be opposite to the one previously assigned.*

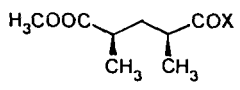
Conglobatin (1) belongs to a group of C_2-symmetrical 16-membered macrodiolides, together with pyrenophorin, vermiculin, and elaiophylin[2]. It was isolated from a culture of *Streptomyces conglobatus* (ATCC 31005)[3] and does not exhibit any of the antifungal, antibacterial, antiprotozoal or antitumor activity of the other members of the group[3]. The constitution and relative configuration of conglobatin was determined by X-ray crystal structure analysis[3], its absolute configuration was inferred[3] by analogy with that of pyrenophorin and vermiculin[4]. The synthesis turned out to be especially challenging due to a) the steric hindrance conveyed by the neighboring methyl substitution to both the secondary OH-group and the carboxylic group of the hydroxyacid from which conglobatin is built, and b) the necessity of forming an oxazole heterocycle as part of the side chain. The following building blocks were used (*Scheme 1*): the *Wittig* reagent derived from methyl 2-bromo-propionate, the (-)-(2S,4R)--2.4-dimethyl-glutaric acid half-ester, N.N-dimethyl-acetamide, and methyl isocyanide.

Scheme 1

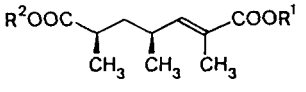


The synthesis is evident from the accompanying *formulae* (*Scheme 2*) of the intermediates 2-16, some properties of which are given in the *Table*, together with reaction conditions, yields, and pertinent references. The first five steps (3 → 8, total yield 45%) were exactly the same as in *Bartlett*'s[5] synthesis of (±)-*Prelog-Djerassi* lactone, except that the enantiomerically enriched half-ester 3 was used, as obtained by *Tamm*'s[6] procedure for the asymmetric hydrolysis of the dimethyl *meso*-glutarate 2 with chymotrypsin. Reaction of the monoester 8

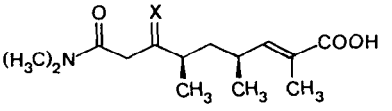
Scheme 2



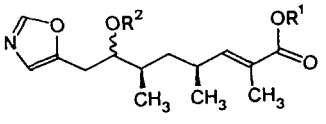
2: X = OCH_3
3: X = OH
4: X = Cl
5: X = H



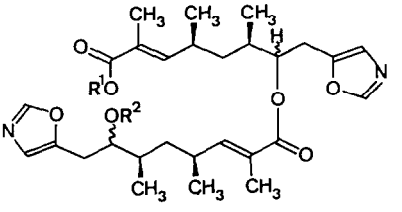
6: $R^1 = R^2 = CH_3$
7: $R^1 = R^2 = H$
8: $R^1 = H$, $R^2 = CH_3$



9 : X = O
10: X = H/OH



11: $R^1 = R^2 = H$
12: $R^1 = CH_2CCl_3$, $R^2 = H$
13: $R^1 = H$, $R^2 = COCH_3$



14: $R^1 = CH_2CCl_3$, $R^2 = COCH_3$
15: $R^1 = H$, $R^2 = COCH_3$
16: $R^1 = R^2 = H$

of trimethyl-hepten-diacid with excess lithium enolate of dimethylacetamide[7] and sodium borohydride reduction of the resulting β-ketoamide 9 gave a 1:1 mixture of epimers 10. The oxazole ring was now constructed by *Schöllkopf*'s method[8]: treatment of 10 with excess lithiated methyl isocyanide - without protection of the OH-groups of the substrate - produced two diastereomers of the octenoic acid 11 (total yield of the three steps 8 → 11: 54%). NMR comparison with the authentic hydroxyacid from cleavage of conglobatin[3] proved that one of the diastereomers 11 was the desired one. Neither at the stage of 10 nor of 11 could we separate the isomers.

At this point, we thought that we had essentially reached the target, since we were sure that we could achieve a dimerizing cyclization - as in the case of all our previous syntheses of C_2-symmetrical macrodiolides[2,4], and even of an unsymmetrical one[9]. This was not the

Table. - *Reaction conditions for the conversions leading to (+)-conglobatin (1) and some characteristic data of the intermediates 2 - 16.*

2: 97%, from the *meso*-anhydride[14] of 2.4-dimethyl-glutaric acid (MeOH/cat. TosOH, 15 h reflux); the (±)-anhydride can be equilibrated (1:1) with the *meso*-form by distillation at 300°.

3: 49% (with 41% recovery of 2), by chymotrypsin ester hydrolysis[6] (pH 8 buffer, 10 d, 20°); $[\alpha]_D$ = -3.7 to -4.3 (77-89% ee); ref.[6] $[\alpha]_D$ = -4.8 (100% ee); the lower ee of our samples became evident also at a later stage of the synthesis, see 11 and 1, below.

4: >98%, from 3 (hexane/$(COCl)_2$, trace of DMF, 1 h, 30°)[5,15], the crude product was used directly for the subsequent step.

5: from 4, by catalytic hydrogenation[5,15] (Pd/C, H_2, 1 atm., in THF, 1.1-equiv. lutidine, 15 h, 20°); the material was used for the *Wittig* reaction without purification.

6: from crude 5 and $(C_6H_5)_3P{=}C(CH_3)COOCH_3$ (CH_2Cl_2, 4 d, 20°); the ylid (m.p. 149-152°) was prepared by heating $(C_6H_5)_3P$ and methyl 2-bromo-propionate ($CHCl_3$, 1 d) and deprotonating with NaOH (*cf.* ref.[5,16]); 6 was hydrolyzed directly to 7.

7: 57% (overall from 3), by 50 min reflux of 6 in MeOH/2 N NaOH; one recrystallization from ether/hexane; $[\alpha]_D$ = +36.6 (c = 5, $CHCl_3$); for (±)-7 see ref.[5].

8: 78%, from 7 [$(CH_3O)_2C(CH_3)_2$/CH_3OH/cat. HCl conc., 60 h, 5°, several h 20° (tlc analysis)[5]].

9: by addition of 8 (in THF) to 4 equiv. of dimethylacetamide enolate (from the amide and LDA[7,17]), from -75° to +20° in THF; colorless oil; one diastereomer by ^{13}C-NMR (keto/enol form 2.5:1 in $CDCl_3$); CH_3-groups of keto-form in ^{1}H-NMR at δ = 1.03, 1.12, 1.30 ppm.

10: 71% (calcd. from 8), by reduction of 9 ($NaBH_4$, EtOH, 2 h, 0°); chromatography (flash column, EtOAc/MeOH, 1% HOAc) also furnished 23% of unreacted 8 (not epimerized at C-6); 10 is a 1:1 mixture of two diastereomers (by ^{13}C-NMR).

11: 76%, by addition of a THF solution of 10 to six equiv. of $LiCH_2NC$[8] (THF, ≤-85° to +10° in 40 min), workup by quenching with CH_3OH (with AcOH, following the original procedure[8]), <5% of 11 was isolated); mixture of (*u*,ℓ)- and (*u*,*u*)-form by ^{13}C-NMR; seeding with an independantly prepared sample of the (±)-(*u*,ℓ)-form gave *ca.* 3% of racemic material (m.p. 117.5-120.0°); this is evidence that the chymotrypsin reaction was not 100% enantioselective (see 3 above); ^{1}H-NMR of 11 ($CDCl_3$, 90 MHz): CH_3-groups at 0.93 and 1.03 ppm, oxazol hydrogens at 6.90 and 7.88 ppm.

12: 61%, from 11, 1.1 equiv. DCC, 3 equiv. Cl_3CCH_2OH, and 0.25 equiv. 4-dimethylamino-pyridine[12] (CH_2Cl_2, 3 h, 20°); ^{1}H-NMR: C=CH at 6.7, COOCH at 3.75 ppm.

13: 69%, from 11, 4 equiv. AcOAc, 5 equiv. pyridine, cat. 4-dimethylamino-pyridine[12] (CH_2Cl_2, 1 d, 20°); the mixed anhydride also formed under these conditions was cleaved by stirring the reaction mixture with conc. aq. NH_4OH for 1 h; ^{1}H-NMR: C=CH at 6.6, COOCH at 5.0 ppm.

14: 95% (calcd. from 12; or 78% calcd. from 13), by stirring a solution of the mixed anhydride from 13 and 2.4.6-trichlorobenzoic acid[11] and 0.8 equiv. of 12 in toluene at 20° for 15 h; ^{1}H-NMR: C=CH at 6.45 and 6.68, COOCH at 5.05 ppm.

16: 79% (overall from 14) by reductive cleavage to 15 (90% aq. AcOH, 10 equiv. Zn dust, 3 h, 0°)[10] and saponification of the acetate (CH_3OH, 8 equiv. K_2CO_3, 2 h, 20°); ^{1}H-NMR: C=CH at 6.45 and 6.58, COOCH at 3.75 and 5.05 ppm.

(+)-Conglobatin (1): By slow addition of the mixed anhydride of 16 and 2.4.6-trichlorobenzoic acid[11] in C_6H_6 (180 ml/mmole 16) to a solution of 16 equiv. 4-pyrrolidino-pyridine in C_6H_6 (1.1 l/mmole 16). Flash chromatography (pentane/ether/EtOAc) gave 10% conglobatin, $[\alpha]_D$ = + 34.5 (c = 1.3, $CHCl_3$), after two crystallizations from ether/hexane $[\alpha]_D$ = +41 (c = 0.26, $CHCl_3$), m.p. 124-126° (ref.[3]: $[\alpha]_D$ = -44 (c = 1, $CHCl_3$), m.p. 125°, a sample of the natural product available to us had m.p. 128.2-128.7°). ^{1}H-NMR (300 MHz) and ^{13}C-NMR of synthetic and natural product are superimposable. - Besides (+)-1, a 14% yield of 8-*epi*-conglobatin was isolated: $[\alpha]_D$ = +9 (c = 1.8, $CHCl_3$), two sets of signals in the ^{1}H- and ^{13}C-NMR spectra (missing C_2-axis!).

case, so that we had to go the long way, converting part of the hydroxyacid to the trichloroethyl[10] ester 12 and part to the acetate 13, coupling the two by esterification with *Yamaguchi*'s method[11] (→ 14), cleaving the trichloroester reductively by *Woodward*'s[10] procedure (→ 15) and the acetate by alkaline saponification (→ 16), all without separation of stereoisomers. The mixture of four diastereomeric *seco*-acids thus obtained (*ca.* 45% from 11) could be cyclized under high-dilution conditions, using again trichloro-benzoylchloride (à la *Yamaguchi*[11]) for activation of the acid group and pyrrolidino-pyridine (a *Steglich* base)[12] for the cyclization step. Of the three possible diastereomeric products of cyclization, two were detected and readily separated by chromatography. All properties of the conglobatin thus isolated (10% from the mixture 16 or 40% of the statistically expected amount) were identical with those of the natural product, except that the sense of the specific rotation was opposite (see bottom of *Table*). Therefore[13], the asymmetric centers of (-)-conglobatin have to be specified (5R,7S,8S,13R,15S,16S), opposite to the previous assignment[3].

References and Footnotes

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