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The Synthesis of the C15-C24 Segment of Ratjadone

Mathias Christmann and Markus Kalesse*

Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, D-30167 Hannover (Germany)

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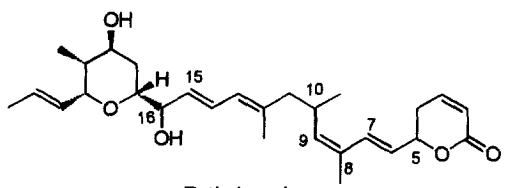
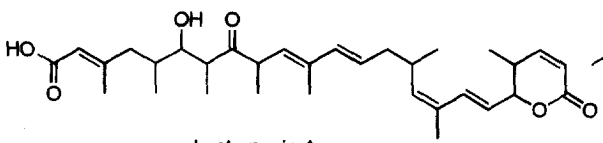
Abstract: Ratjadone is an antifungal and highly cytotoxic polyketide from *Sorangium cellulosum*. The tetrahydropyran ring is supposed to result from an intramolecular opening of a C16-C17 epoxide. Herein we report the biomimetic synthesis of the C15-C24 segment of ratjadone.

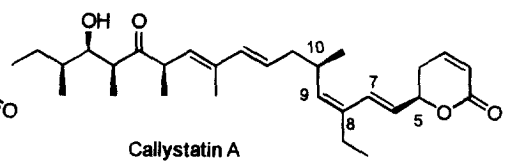
Ratjadone (**1**) was discovered in 1994 by Schummer, Gerth, Reichenbach and Höfle from *Sorangium cellulosum* collected as a soil sample at Cala Ratjada (Mallorca, Spain).[1] It belongs to a family of polyketides which include leptomycin,[2] kazusamycin,[3] anguinomycin,[4] leptofuranin[5] and callystatin A.[6] These substances possess a high cytotoxity along with other interesting biological effects (*e.g.* changes in the cell morphology).[2b]



Ratjadone **1**



Leptomycin A



Callystatin A

Our goal is the synthesis of ratjadone and the identification of the pharmacologically relevant substructures. Additionally, the synthesis can provide crucial information to determine the absolute stereostructure of ratjadone. Since the relative stereochemistry at C5, C10 and C16 and the absolute configuration of ratjadone were not known at the outset of this synthesis it was necessary to design a flexible strategy allowing for the eventual formation of all possible stereoisomers.[7] Ratjadone is a typical polyketide produced by head to tail condensations of acetate and propionate units.

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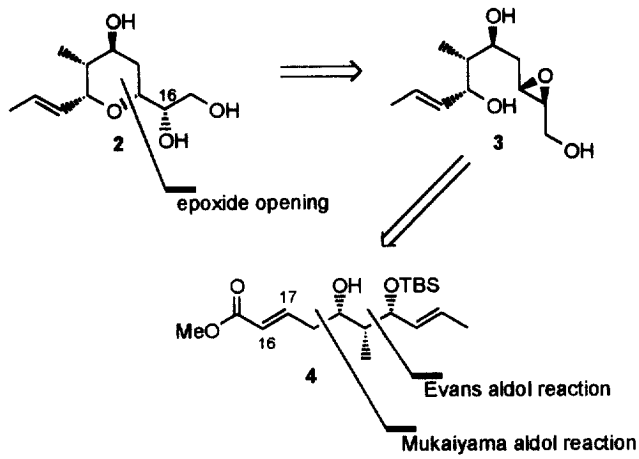


Figure 1:

The nonregular position of the C16 oxygen was supposed[2a] to result from an intramolecular opening of a C16-C17 epoxide as shown for other polyketide antibiotics in experiments under ^{18}O-atmosphere.[8] For the synthesis of the C15-C24 (**2**) segment we decided to use a biomimetic approach which is outlined in figure 1.

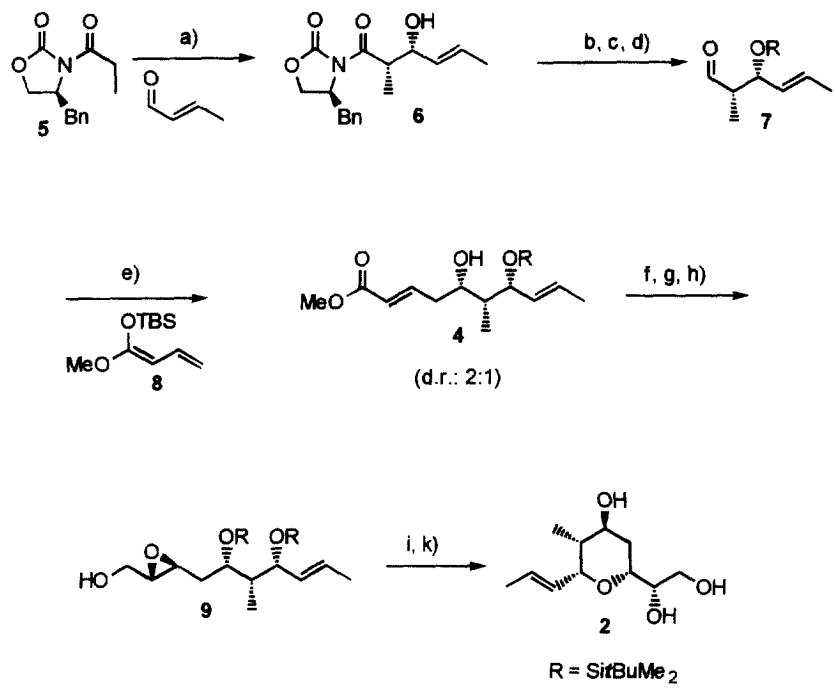
Retrosynthetic disassembly of the tetrahydropyran ring leads to epoxide **3** which can in synthetic direction take part in a 6-*exo* epoxide cyclization.[9] The key steps in the synthesis of the carbon skeleton (**4**) are an Evans asymmetric aldol reaction and a vinylogous Mukaiyama aldol reaction. After the introduction of the asymmetry *via* the Evans auxiliary, which is commercially available in both antipodes, no further chiral auxiliary is needed. It is noteworthy that the configuration at C16 can be controlled by the C16-C17 double bond geometry.

The synthesis commences with an Evans aldol reaction between imide **5** and crotonaldehyde.[10] The hydroxyl group was protected as its *tert*-butyldimethylsilyl ether with *tert*-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine. Reductive removal of the auxiliary with lithium borohydride followed by pyridinium chlorochromate (PCC) oxidation furnished aldehyde **7** in 62 % yield over three steps. The vinylogous Mukaiyama aldol reaction[11] of aldehyde **7** and silyl ketene acetal **8** provided the aldol adduct **4** in 42 % yield as a 2:1 mixture in favour of the desired *syn*-isomer.

The diastereomeric alcohols were easily separated by flash chromatography. We are confident that with some experimentation we are able to increase the yield and the diastereomeric excess of this reaction.

After silylation of the hydroxyl group with TBSOTf the α,β-unsaturated ester was reduced to its corresponding allylic alcohol with diisobutylaluminium hydride. Since Sharpless asymmetric epoxidation was reported to give poor selectivity for related compounds we used the conditions employed by Saito[12] and Nakata.[13] Epoxidation with *meta*-chloroperoxybenzoic acid provided epoxide **9** as a single diastereomer. The other double bond was left unaffected under this conditions. When the fluoride-induced cleavage of the *tert*-butyldimethylsilyl ethers

with tetra-*n*-butylammonium fluoride (TBAF) was complete as indicated by TLC, amberlyst-15 (H^+)[14] was added and the cyclization occurred smoothly within 12 h to yield **2** in 93% yield.[15]



Scheme 1: a) nBu$_2$BOTf, Et$_3$N, CH_2Cl_2, 78 %; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C; c) $LiBH_4$, THF, 0 °C; d) PCC, CH_2Cl_2, r.t., three steps 62 %; e) BF_3 OEt_2, CH_2Cl_2, Et_2O, -78 °C, 42 %; f) TBSOTf, 2,6-lutidine, -78 °C; g) Dibal-H, THF, -78 °C; h) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, three steps 85 %; i) TBAF, THF, r.t., k) amberlyst-15, 93 %.

The diastereomeric alcohols were easily separated by flash chromatography. We are confident that with some experimentation we are able to increase the yield and the diastereomeric excess of this reaction.

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In conclusion we have presented a concise approach to the tetrahydropyran C15-C24 subunit. The total synthesis of ratjadone will be reported in due course.

References and Notes

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15. The configuration of the THP ring was assigned using extensive NOESY and COSY studies. **2**: ^{13}C-NMR(100 MHz, $CDCl_3$): δ=129.9, 126.8, 74.8, 74.2, 73.5, 70.0, 63.5, 39.6, 29.1, 17.9, 11.2; ^{1}H-NMR(400 MHz, $CDCl_3$): δ=5.64 (ddq, *J*=15.4, 1.4, 6.5, 1H), 5.40 (ddq, *J*=15.4, 6.0, 1.6, 1H), 4.39 (m, 1H), 3.99 (q, *J*=2.9, 1H), 3.94 (ddd, *J*=12.3, 4.4, 1.5, 1H), 3.61-3.78 (m, 3H), 1.78 (dt, *J*=14.1, 12.3, 2.9, 1H), 1.78 (t, *J*=6.5, 1.4, 3H), 1.68 (m, 1H), 1.50 (m, 1H), 0.89 (d, *J*=7.2, 3H); IR($CHCl_3$): ν=3682, 3609, 3470, 2929, 1079, 1050 cm^{-1}; MS(EI): m/z=216[M$^+$], 155, 137, 111, 83, 71; HRMS: $C_{11}H_{22}O_4$ [M$^+$]: found: 216.1364 calc.: 216.1362; α^{20}_D=2.0 (c=1, $CHCl_3$).