sodium, and four of the oxygen atoms can be described in a monoclinic space group, and the unit cell can be transformed accordingly into a monoclinic one. Only one oxygen position is not consistent with this cystallographic description. The knowledge of the structure of the isotypic compound Na_4MoO_5,[11] however, substatiates the structure analysis and clarifies the observed pseudosymmetry in favor of the low symmetry space group in the triclinic system.

Experimental Section

$Na_6Se_2O_9$ was prepared by the solid-state reaction of Na_2O with Na_2SeO_4 in a molar ratio of 1:2 in a closed silver crucible sealed in a glass ampule. Na_4SeO_5 was prepared by the solid-state reaction of Na_2O with Na_2SeO_4 in a molar ratio 1:1 in a sealed silver tube under a pressure of 2.5 GPa (piston-cylinder-press[12]). In both cases, the reaction time was two days and the reaction temperature was 500 °C. Na_2O was prepared according to reference [13], and Na_2SeO_4 (purum p.a. > 99 %, Fluka) was dried under vacuum prior to reaction (10^{-3} mbar, 400 °C, 24 h).

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Total Synthesis of (+)-Ratjadone**

Mathias Christmann, Ulhas Bhatt, Monika Quitschalle, Eckhard Claus, and Markus Kalesse*

Ratjadone (**1**) was isolated in 1994 by Höfle et al. from *Sorangium cellulosum* (So ce360) collected as a soil sample at Cala Ratjada (Mallorca, Spain).[1] It is similar in both structure and its biological profile to polyketides like leptomycin,[2] callystatin A,[3] and other related compounds.[4] Ratjadone shows high cytotoxicity in cultured mouse cell lines (L929) with an IC_{50} value of 50 pg mL^{-1} and it inhibits the growth of the HeLa cell line (KB3.1) at remarkably low concentrations (40 pg mL^{-1}). In addition, it shows other interesting biological effects (e.g. changes in the cell morphology and growth of yeast) and a narrow spectrum of antifungal activity with MIC values (MIC = mimimal inhibiting concentration) ranging from 0.04 to 0.6 μg mL^{-1} for *Mucor hiemalis*, *Phythophthora drechsleri*, *Ceratocystis ulmi*, and *Monila brunnea*.[5] Despite these promising biological properties, neither the exact mode of action nor the molecular targets are known.

Here we report the first total synthesis of ratjadone.[6] Our highly convergent approach allows the rapid assembly of various ratjadone derivatives for the identification of biologically active substructures. Since only the relative stereochemistry of the tetrahydropyran moiety (C17 – C21) was known at the outset of this synthesis, it was necessary to design a flexible strategy that would allow the formation of all possible stereoisomers.[7] The structure of ratjadone reveals the diene systems as attractive sites for the retrosynthetic disassembly (Scheme 1). We dissected ratjadone into three fragments, the tetrahydropyran subunit **A**, the phosphonium salt **B**, and the aldehyde **C**. In the synthesis, fragments **B** and **C** were joined by a Wittig reaction followed directly by a Heck coupling for the connection with the **A** fragment.

The synthesis of **A** began with the transformation of the known aldol product **2**[8] into the Weinreb amide[9] followed by protection of the hydroxy group (TBS) and subsequent reduction with Dibal-H to generate aldehyde **3** (Scheme 2). The all-*syn* stereo triad (C19, C20, C21) of the **A** fragment was generated by a vinylogous Mukaiyama aldol reaction.[10] The reaction of **3** with the ketene acetal **4** and $BF_3 \cdot OEt_2$ as the Lewis acid gave the α,β-unsaturated ester **5** with a selectivity of 3:1 in favor of the desired Felkin – Ahn product. After silylation of the hydroxy group and reduction of the ester functionality, the allylic alcohol **6** was diastereoselectively epoxidized ($de > 95$ % in favor of the *anti* isomer) with *m*CPBA.[11] Removal of the TBS protecting groups with TBAF was followed by treatment with amberlyst-15 to induce the intramolecular 6-*exo* ring closure.[12] This key step generates

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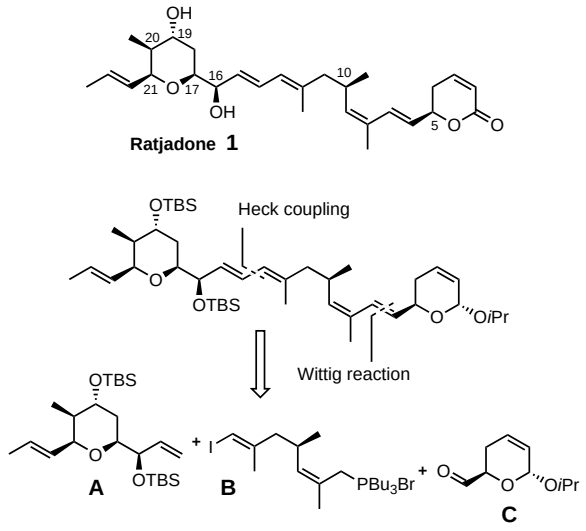
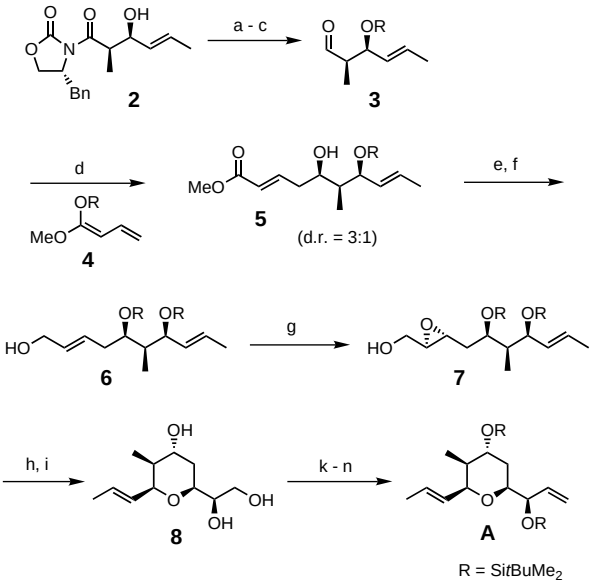


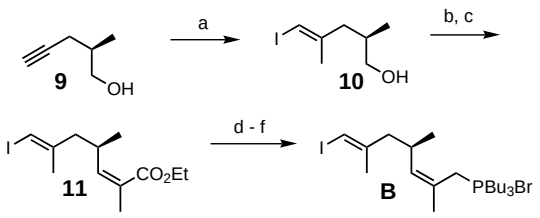
Scheme 1. Retrosynthetic analysis of ratjadone. TBS = *tert*-butyldimethylsilyl.



Scheme 2. Synthesis of the **A** fragment. a) MeONHMe·HCl, Me_3Al, CH_2Cl_2, −20→25 °C; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; c) Dibal-H, THF, −78 °C, 83% (over three steps); d) $BF_3 \cdot Et_2O$, CH_2Cl_2, Et_2O, −78 °C, 67%; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; f) Dibal-H, THF, −78 °C; g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 85% (over three steps); h) TBAF, THF, 88%; i) amberlyst-15, THF, 93%; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 87%; l) $CHCl_3 \cdot HCl$, 97%; m) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 92%; n) Tebbe reagent, THF, 0 °C, 95%. Dibal-H = diisobutylaluminum hydride; *m*CPBA = *m*-chloroperoxybenzoic acid; TBAF = tetra-*n*-butylammonium fluoride; TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate; Tebbe reagent = $[Cp_2Ti(\mu\text{-}CH_2)(\mu\text{-}Cl)AlMe_2]$.

the tetrahydropyran moiety in fragment **A** and also establishes the C16-OH in *R* configuration. Protection of all three hydroxy groups (TBS) and treatment with acidic $CHCl_3$[13] liberated the primary hydroxy group selectively, whose oxidation with Dess–Martin periodinane[14] followed by olefination with the Tebbe reagent[15] provided the **A** fragment.

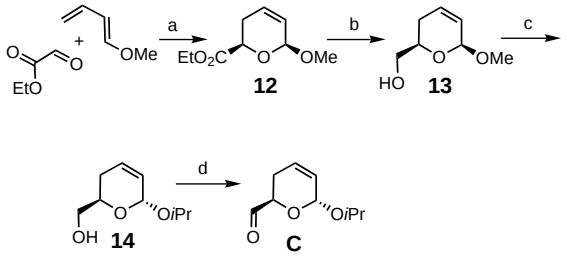
The synthesis of the **B** fragment commences with alkyne **9**,[16] derived from (*S*)-3-hydroxyisobutyric acid (Scheme 3). Carbometalation of **9** and subsequent quenching with iodine



Scheme 3. Synthesis of the **B** fragment. a) $[Cp_2ZrCl_2]$, $AlMe_3$, I_2, CH_2Cl_2, THF, −15 °C→25 °C, 83%; b) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 81%; c) $(CF_3CH_2O)_2P(O)CHMeCO_2Et$, KHMDS, [18]crown-6, THF, −78 °C, 85%; d) Dibal-H, CH_2Cl_2, −78 °C, 77%; e) CBr_4, Ph_3P, CH_3CN; f) Bu_3P, CH_3CN, 87% (over two steps). KHMDS = potassium hexamethyldisilazanide.

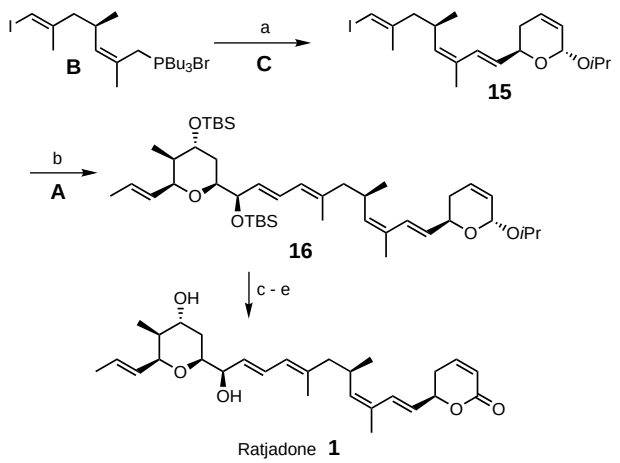
according to the protocol developed by Negishi et al.[17] generated vinyl iodide **10**. The trisubstituted *Z*-double bond was introduced by Dess–Martin oxidation, followed by Still–Gennari olefination.[18] After the reduction of the ester **11** with Dibal-H, the allyl alcohol was initially transformed into a bromide (CBr_4, PPh_3) and then converted to the corresponding phosphonium salt **B** with tributylphosphane.[3b]

The key step in the construction of fragment **C** is a hetero-Diels–Alder reaction[19] between 1-methoxy butadiene and ethyl glyoxolate in which the chiral Lewis acid generated from (+)-BINOL and $Ti(OiPr)_4$ was used as catalyst (10 mol%) (Scheme 4). The hetero-Diels–Alder reaction generated compound **12** as a mixture of *endo* and *exo* adducts (56% *de* for the *endo* adduct) in high enantioselectivity (>90% *ee*); the desired *R* configuration at C5 was favored in both diastereomers. Reduction of the resulting ester with $LiAlH_4$ furnished alcohol **13**. During the course of our investigations it became clear that the β-anomer led to substantial epimerization at C5 in the Wittig reaction of aldehyde **C**. We therefore converted the β-anomer into the thermodynamically more stable α-anomer (**14**) by substituting the methoxy group for an isopropyloxy group.[20] Swern oxidation[21] of **14** then established fragment **C** in 50% overall yield.



Scheme 4. Synthesis of the **C** fragment. a) $Ti(OiPr)_4$, (+)-BINOL, 4-Å molecular sieves, CH_2Cl_2, 65%; b) $LiAlH_4$, Et_2O, 0 °C; c) *i*PrOH, PPTS; d) Swern oxidation, 77% (over three steps). BINOL = 2,2′-dihydroxy-1,1′-binaphthyl; PPTS = pyridinium *p*-toluenesulfonate.

Now the stage was set for coupling the individual fragments (Scheme 5). The Wittig[3c,d] reaction between the aldehyde **C** and the phosphonium salt **B** in toluene using *t*BuOK as base gave the vinyl iodide **15** in 76% yield. Compound **15** was then coupled to the **A** fragment by a Heck reaction.[22] In this transformation the Jeffery conditions[23] (phosphane-free) were superior to a variety of other Pd^0 sources such as



Scheme 5. Coupling of the three fragments. a) *t*BuOK, toluene, 0 °C, 76 %; b) $Pd(OAc)_2$, Bu_4NBr, Cs_2CO_3, Et_3N, DMF, 65 %; c) acetone/H_2O, PPTS, 83 %; d) TPAP, NMO, MS 4 Å, CH_2Cl_2, 77 %; e) HF · py, THF, py, 76 %. NMO = *N*-methylmorpholine-*N*-oxide; Py = pyridine; TPAP = tetra-*n*-propylammonium perruthenate.

$[Pd(PPh_3)_4]$ and $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and provided **16** selectively. Acetal **16** was hydrolyzed under mild acidic conditions (PPTS, acetone, H_2O), and the resulting hemiacetal was oxidized to the α,β-unsaturated lactone by using TPAP/NMO.[24] Attempts with standard TBS deprotection reagents (TBAF, tris(dimethylamino)sulfur – trimethylsilyl difluoride (TASF), and HF · pyridine) were unsuccessful. Only HF · pyridine in THF/pyridine[2d] as the solvent gave clean conversion to ratjadone.

Comparison of the spectroscopic data (^{1}H NMR, circular dichroism (CD), optical rotation) of the synthetic compound with that of the natural product[25] showed that both compounds were identical. It can be concluded that the previously unknown configurations at C5, C10, and C16 have the *R* configuration.[26] The highly convergent total synthesis of ratjadone described herein has 18 linear steps and gives 6.8 % overall yield. In addition, the intermolecular Heck reaction has been demonstrated to be an attractive alternative to Stille and Suzuki couplings in the total syntheses of complex natural products. With this reliable synthetic route we are now in a position to synthesize structural analogues with which the various cellular processes mediated by ratjadone can be probed.[27]

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[27] In preliminary biological testings we found discrepancy in the cytotoxicity of natural and synthetic ratjadone. M. Christmann, U. Bhatt, M. Quitschalle, E. Claus, M. Kalesse, unpublished results.

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