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Synthesis of the C_6-C_{16} Polyene Fragment of Ratjadone, a Potent Cytotoxic Metabolite from *Sorangium cellulosum*

Eckhard Claus and Markus Kalesse*

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

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Abstract: The Pd-catalyzed synthesis of the polyene fragment of ratjadone is described. This strategy employs the Stille-coupling for the coupling of the tetrahydropyran subunit and the Suzuki coupling for attaching the unsaturated lactone to the polyene chain.

Ratjadone[1] belongs to a family of polyketides, which include leptomycins,[2] callystatins[3] and anguinomycins[4] (Scheme 1). Only little is known about the biological targets of these so-called orphan ligands.[5] The first indications about the mode of action of these compounds came from biological investigations of leptomycin (**3**).[6] It has been found, that these compounds inhibit the function of the *crm1* gene, which is required for maintenance of the chromosome structure and correct gene expression in fission yeast.[7] The characteristic of these compounds is a polyene chain connecting an unsaturated lactone with an aldol fragment. In ratjadone, this aldol fragment is substituted by a tetrahydropyran subunit, resembling the aldol structure of related compounds.

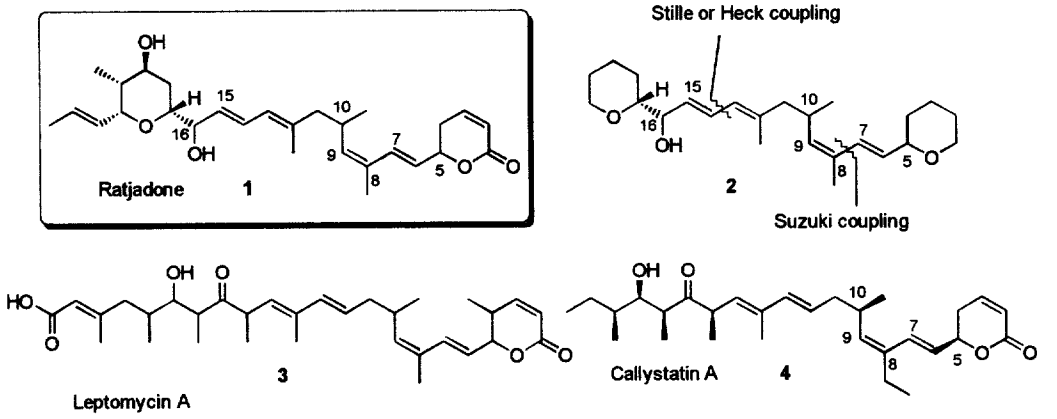

Figure 1. Structures of ratjadone, callystatin A and leptomycin A and the ratjadone model compound **2**.

Our goal is to establish an efficient route for the synthesis of ratjadone and its derivatives that allows the incorporation of subunits in both enantiomeric forms in order to determine the biological active subunits. Even though the configurations at C5 and C10 have not been determined, we expect from comparison of ratjadone (**1**) to callystatin A (**4**) C5 and C10 to be in the *R* configuration. For that reason we incorporated in the synthesis of

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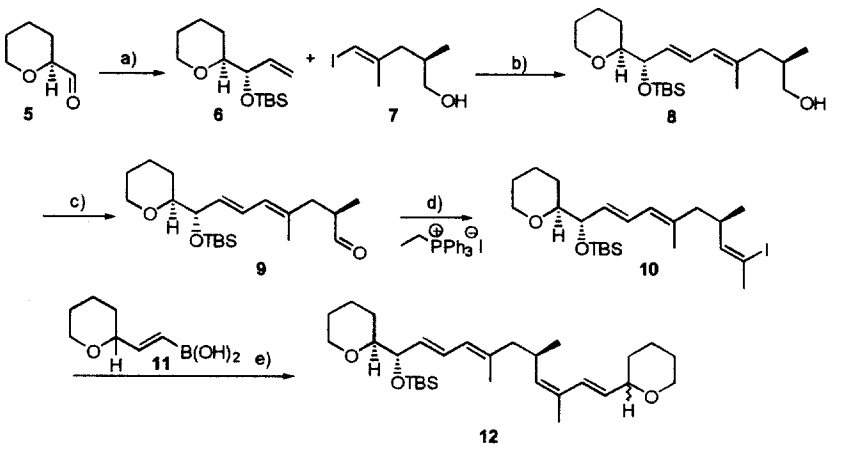
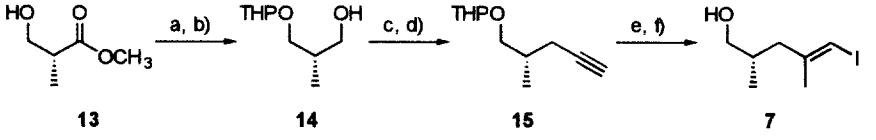
the polyene fragment the asymmetric center derived from enantiomerically pure (R)-(-)-3-hydroxyisobutyric acid (**13**) (Scheme 2). In our approach the retrosynthetic disconnections are placed between C13 and C14 and between C7 and C8 (Figure 1). In order to establish the coupling reactions between the three different subunits we began the synthesis with tetrahydro-pyran-2-carbaldehyde (**5**) as the tetrahydropyran model compound (Scheme 1). Addition of vinyl magnesium bromide and TBS protection generated **6** in a 4:1 ratio with the threo-isomer as the major compound.[8] Heck coupling[9] with the unprotected vinyl iodide **7** gave alcohol **8**. Oxidation of **8** with the Dess-Martin periodinane followed by a Wittig[10] reaction generated vinyl iodide **10**. Finally the Suzuki coupling[11] with vinyl borane **11** (Scheme 3) gave product **12** with the desired polyene chain of ratjadone. Subsequent liberation of the TBS-protected alcohol generates the ratjadone model compound **2**.[12]



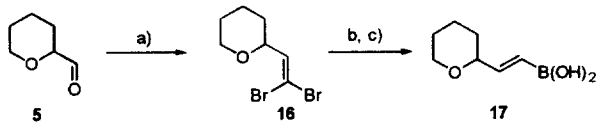
Scheme 1: Synthesis of the ratjadone model compound **2**: a) 1. Vinyl magnesium bromide, THF, 1h, 0 °C, 2. TBSCl, Et_3N, DMAP, CH_2Cl_2, 42h, r.t., 65 % two steps; b) $Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF, 3h, r.t., 47 %; c) Dess-Martin periodinane, CH_2Cl_2, 0 °C→r.t., 80%; d) *n*-BuLi, I_2, NaHMDS, THF, 15min, -20 °C, 48 %; e) $Pd(PPh_3)_4$, THF, NaOH, H_2O, 3h, reflux, 59 %.

Compound **7** was synthesized optically active from hydroxyisobutyric acid (**13**) (Scheme 2). THP protection of **13** followed by $LiAlH_4$ reduction generates **14**. Tosylation and subsequent addition of the lithium salt of TMS-acetylene establishes compound **15**. The THP ether was deprotected with Amberlite® IR-200 and iodo methylation generates vinyl iodide **7**.



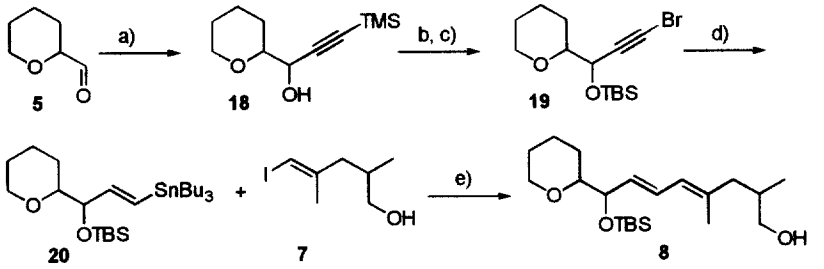
Scheme 2: Synthesis of optically active vinyl iodide **7**: a) DHP, TsOH, THF, r.t., 54 %; b) $LiAlH_4$, THF, r.t., 85%; c) TsCl, DMAP, pyridine, CH_2Cl_2, 20h, r.t., 90%; d) Li-acetylene-EDA, DMSO, 4h, r.t., 52%; e) Amberlite® IR-120, MeOH, 24h, r.t., 42%; f) Cp_2ZrCl_2, $AlMe_3$, I_2, CH_2Cl_2, THF, 15h, -15 °C→r.t., 83%.

The vinyl borane **17** was also synthesized from tetrahydro-pyran-2-carbaldehyde (**5**) by a sequence of the Corey-Fuchs reaction and hydroboration with catechol borane (Scheme 3).



Scheme 3: Synthesis of the vinyl borane **17**: a) CBr_4, PPh_3, NEt_3, CH_2Cl_2, -60 °C→r.t., 85%; b) *n*-Buli, Et_2O, 1h, -78 °C, 73%; c) catechol borane, 1.5h, 70 °C, 35%.

Alternatively to the Heck procedure the coupling between the tetrahydropyran unit and vinyl iodide **7** could also be accomplished via the Stille[13] procedure. The Stille procedure was superior to the Heck coupling on small scale reactions but the yields dropped when reactions in larger quantities than 10 mM were coupled.



Scheme 4: Stille coupling to yield fragment **8**: a) TMS acetylene, THF, -78 °C, 1h, 70%; b) 1. TBSCl, Et_3N, DMAP, CH_2Cl_2, 42h, r.t., 91 %, 2. K_2CO_3, MeOH, 5h, r.t., 98%; c) NBS, $AgNO_3$, acetone, 2h, r.t., 91%; d) $Pd(PPh_3)_4$, Bu_3SnH, THF, 1h at –78 °C then r.t., 85%; e) $Pd(PPh_3)_4$, THF/DMF 1:1, 5h, 60°C, 42%.

The vinyl stannane precursor for the Stille coupling was synthesized by addition of TMS acetylene to **5**. Protection of the secondary alcohol, transformation into the bromo acetylene **19** and hydrostannylation establishes the vinyl stannane **20**. Stille coupling with $Pd(PPh_3)_4$ generates compound **8** which can be transformed to model compound **2** accordingly.

The synthesis of ratjadone and the biological activity of ratjadone derivatives will be reported in due course.

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12. **2**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 6.55 (dd, J = 15.6 Hz, J = 5.9 Hz, 1H), 6.44 (dd, J = 14.8 Hz, J = 10.7 Hz, 1H), 5.78 (m, 1H), 5.63 (dd, J = 16.0 Hz, J = 6.3 Hz, 1H, diastereomer), 5.62 (dd, J = 15.6 Hz, J = 6.5 Hz, 1H), 5.56 (dd, J = 15.3 Hz, J = 6.7 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H, diastereomer), 5.10 (d, J = 8.9 Hz, 1H), 4.13 (m, 1H), 4.01 (m, 2H), 3.85 (m, 1H), 3.46 (m, 2H), 3.35 (m, 1H), 2.79, 2.00 (m, 3H), 1.90-1.20 (m, 12H), 1.75 (s, 3H), 1.71 (s, 3H), 0.87 (m, 3H); MS (100°C): 374 (1.77) [M^+], 290 (2.36), 256 (2.88), 180 (11.12), 179 (14.62), 167 (6.45), 149 (15.54), 119 (3.71), 109 (11.85), 96 (10.64), 85 (100) [THP], 73 (5.35), 70 (15.06), 67 (10.74); HRMS: $C_{24}H_{38}O_3$ [M^+]: found.: 374.282095 calcd.: 374.282166.
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