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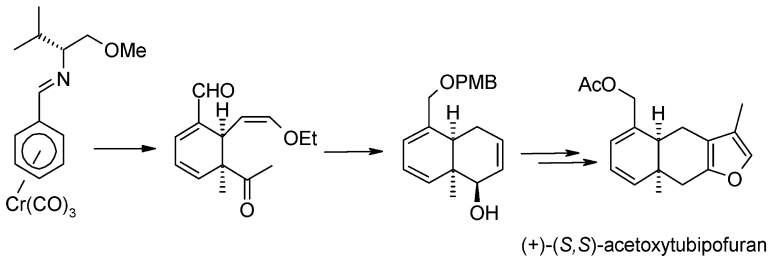

(+)-(*S*,*S*)-acetoxytubipofuran

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Chromium-Mediated Asymmetric Synthesis of Both Enantiomers of Acetoxytubipofuran

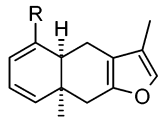
E. Peter Kündig,* Rita Cannas, Mundruppady Laxmisha, Liu Ronggang, and Sylvie Tchertchian

Department of Organic Chemistry, University of Geneva, 30 Quai Ernest Ansermet, 1211 Geneva 4, Switzerland

Received December 30, 2002; E-mail: peter.kundig@chiorg.unige.ch

Tricarbonylchromium-mediated dearomatization provides an efficient direct access to substituted cyclohexadienes.[1]Up to three C-substituents can be added in a regio- and stereoselective manner across an arene double bond in a one-pot sequence. We here report new aspects of this reaction in the context of an application to the asymmetric synthesis of both enantiomers of acetoxytubipofuran.

The furanoterpenes tubipofuran (**1**) and acetoxytubipofuran (**2**) were isolated from the Japanese stolonifer *Tubipora musica* Linnaeus in 1986 and were shown to be eudesmane-type marine furanosesquiterpenoids having a cis-fused decalin ring with a homoannular 1,3 diene system.[2]The compounds show ichtiotoxicity



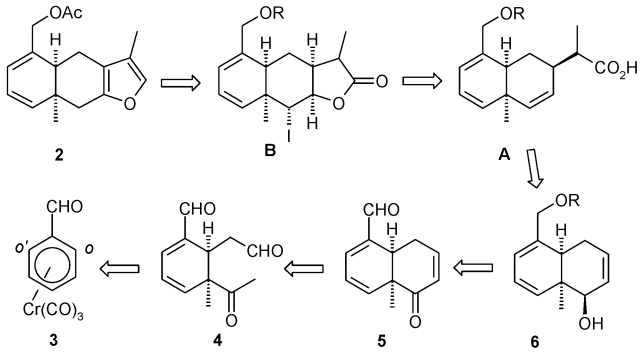
1: R = CH_3
2: R = CH_2OAc

toward killifish (*Orizias latipes*), and 15-acetoxytubipofuran (**2**) shows cytotoxicity against B-16 melanoma cells in vitro (IC_{50} 33 μg/mL). On the basis of the diene helicity rule, the 4a*S*,8a*R* absolute configuration was originally assigned to (+)-**1** but the work of Pedro and co-workers, who converted santonin into tubipofuran, showed that this has to be revised and that tubipofuran (+)-**1** has the 4a*R*,8aS absolute configuration as shown here.[3]A racemic synthesis of the tubipofurans was reported by Kanematsu and co-workers in 1994.[4]

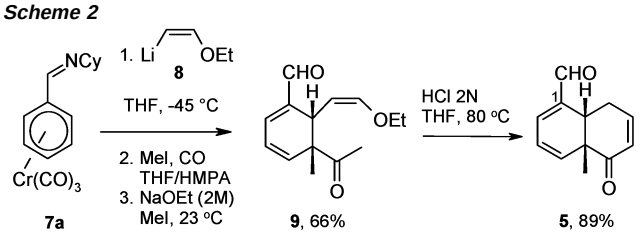
Given the absence of an asymmetric synthesis of **2** and the synthetically interesting *cis*-fused cyclohexadiene with two adjacent stereogenic centers, one of them a quaternary one, we initiated a project of synthesis (Scheme 1). An aromatic precursor to the *cis*-fused ring system integrating a 1,3-cyclohexadiene would be an attractive route provided that the absolute configuration of the two stereogenic centers can be controlled. Retrosynthetically, formation of the furan ring in **2** via iodolacton **B** requires the decalin-acetic acid intermediate **A**. This in turn may be formed either via Pd-catalyzed allylic alkylation or via Claisen rearrangement from **6**, in turn obtained by reduction from **5**. In the forward direction, for the synthesis of cyclohexadiene enone **5** we require the addition of an acetaldehyde fragment to the ortho position of [(benzaldehyde)-$Cr(CO)_3$] (**3**) followed by a regioselective and diastereoselective acylation/alkylation at C(5).

In a preliminary study we established the feasibility of the transformation of benzaldehyde complex **3** into **5**. ortho-Addition of ethoxyvinyl Li[5] (**8**) to the imine complex **7a**,[6] followed by acylation/alkylation and imine hydrolysis gave **9** with the correct relative configuration (Scheme 2, eq 1).[7] Enol ether hydrolysis and intramolecular aldol condensation afforded **5** with the anticipated *cis*-decalin skeleton.

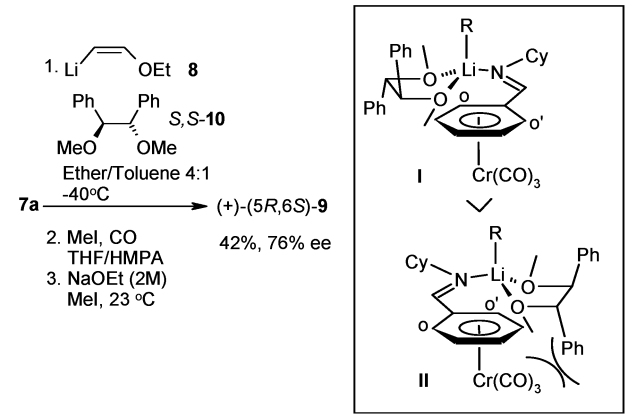
Scheme 1



Scheme 2



Scheme 3



For the synthesis of (4a*R*,8a*S*)-**5** we chose an enantioselective nucleophile addition of **8** to complex **7a** in the presence of the diether *S*,*S*-**10**. Enantiomeric excess values in the lower 90th percentiles had been obtained previously with this method when toluene was used as solvent.[8] The need for diethyl ether as solvent in the generation of **8** (bromide/lithium exchange) and this nucleophile's low thermal stability resulted in an erosion of both enantioselectivity and yield (Scheme 3). Fortunately, recrystallization of the fused diene−enone (4a*R*,8a*S*)-**5** afforded a highly enantioenriched product (>99% ee).

A rationale of observed enantioselectivity of nucleophilic addition is shown above, and preference of addition to the ortho, rather than

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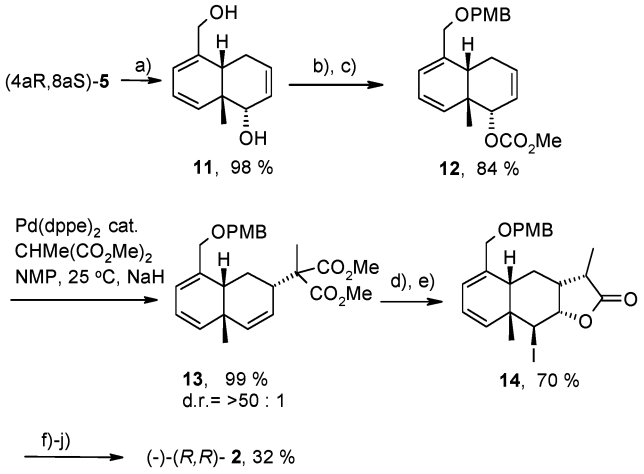
Scheme 4 [a]



[a] (a) $NaBH_4$, $CeCl_3$, MeOH, 98%; (b) NaH, PMBI, DMF, 88%; (c) $ClCO_2Me$, py, CH_2Cl_2, 95%; (d) 6 M NaOH, DMSO, 130 °C, 93%; (e) I_2, KI, $NaHCO_3 \cdot H_2O/CH_2Cl_2$: 94%; (f) Bu_3SnH, AIBN, tol, reflux, 91%; (g) 1. LDA/PhSeCl, 2. H_2O_2 66%; (h) DDQ, 1.3 equiv, CH_2Cl_2/H_2O, 80%; (i) 1. DIBAL, tol, −40 °C 2. AcOH, 73%; (j) Ac_2O, py, DMAP, CH_2Cl_2, 92%.

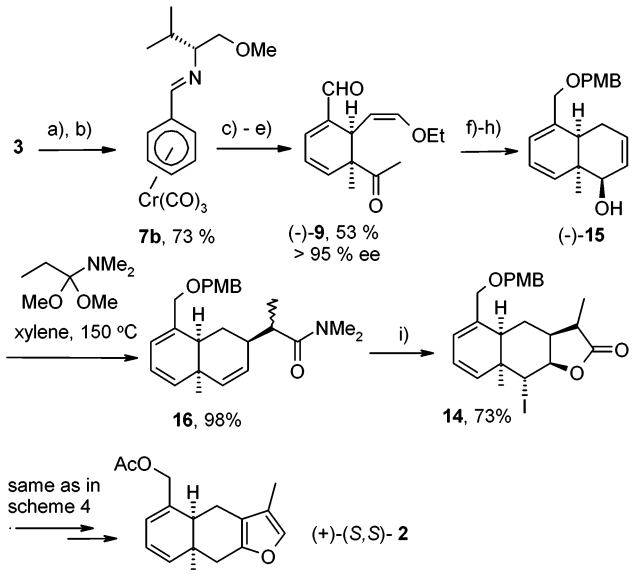
to the ortho′ position is based on steric congestion state between a Ph group of the chiral ligand and the $Cr(CO)_3$ group in transition state **II**.

Reduction of (4a*R*,8a*S*)-**5** under Luche conditions afforded diol **11** as a single diastereoisomer with the hydride adding to the ketone from the less hindered, convex face of the molecule.[9] Selective protection of the primary alcohol as *p*-methoxybenzyl ether and conversion of the secondary alcohol into the carbonate **12** set the stage for the Pd-catalyzed allylic alkylation. The reaction with $NaCMe(CO_2Me)_2$ in the presence of $Pd(dppe)_2$ afforded regioselectively the product resulting from addition to C(7), and overall retention was the major pathway. The ratio of the diastereoisomers **13** at C(7) was 50:1. The transformation of **13** into acetoxytubipofuran **2** is depicted in Scheme 4, and details are given in the Supporting Information.

As mentioned above, the conversion of santonin into (+)-tubipofuran required a reassignment of the absolute configuration in the natural product.[3] Moreover, the observed $[\alpha]_D^{20}$ value was much larger (33) than that reported earlier (5.6), suggesting that the natural product isolated may not have been pure. A parallel situation exists for acetoxytubipofuran **2**. The natural product was assigned the *R*,*R*-configuration and its $[\alpha]_D^{20}$ value reported as +10.7 ($c = 0.5$, $CHCl_3$). Our measured value for (*R*,*R*) is −120 ($c = 0.653$, $CHCl_3$) and the CD spectrum showed a negative Cotton effect λ_{max} 274 ($\Delta\epsilon$ −3), opposite to that reported (λ_{max} 270 ($\Delta\epsilon$ +3)).[2a]

In parallel to the synthesis of (−)-**2**, we have developed a modified route to the natural product (+)-**2**. Condensation of the benzaldehyde complex **3** with D-valinol[10] followed by in situ methylation gave the chiral arylimine complex **7b** (Scheme 5). Diastereoselective nucleophilic addition/acylation/alkylation yielded (−)-(4a*S*,8a*R*)-**9**. Both the yield and the enantiomeric purity of the product were superior to the procedure used for the keto aldehyde (+)-(4a*R*,8a*S*)-**9**. Conversion of (+)-**9** by the same route as detailed before (Schemes 2 and 4) afforded (−)-**15**. The four-step sequence of formation of carbonate, Pd-catalyzed allylic substitution, hydrolysis/decarboxylation, and lactonization that was used in the synthesis of (*R*,*R*)-**2** was replaced now by the very efficient Eschenmoser−Claisen rearrangement−lactonization sequence[11,12] which afforded **14** as a 3:2 mixture of diastereoisomers. From here

Scheme 5 [a]



[a] (a) D-Valinol, Et_2O, rt; (b) NaH, MeI, THF, rt, 73% (a, b one pot); (c) **8**, THF, −78 °C; (d) HMPA, MeI, 5 bar CO, −78 °C to rt; (e) NaOEt, MeI, −78 °C to rt, 53% (c−e one pot); (f) HCl 2N, THF, 80 °C, 89%; (g) $NaBH_4$, $CeCl_3$, MeOH, 98%; (h) NaH, PMBI, DMF, 88%; (i) I_2, THF, H_2O, 73%.

on the synthesis followed that shown in Scheme 4. (*S*,*S*)-Tubipofuran ((*S*,*S*)-**2**) showed a $[\alpha]_D^{20}$ of +100.3 ($c = 0.29$, $CHCl_3$).

In summary, this Communication reports new asymmetric methodology of $Cr(CO)_3$-mediated dearomatization and its application to the synthesis of (+)- and (−)-acetoxytubipofuran. Chiroptical data show that a revision of the assigned structure of the natural product is required.

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Supporting Information Available: Experimental procedures and physical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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