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Synthesis of (-)-Erythrodiene *via* Intramolecular Pd-Catalyzed Zn-Ene Reaction

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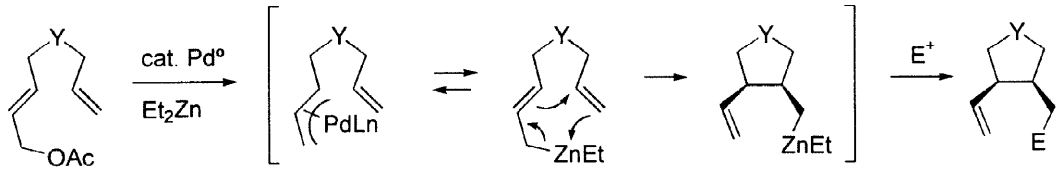
Abstract

A highly diastereoselective synthesis of (-)-Erythrodiene was achieved *via* an intramolecular Pd-catalyzed Zn-ene reaction as the key step. It was found that $Pd(OAc)_2/Bu_3P$ was a superior catalyst for this reaction to $Pd(PPh_3)_4$.

Keywords: *Spiro compounds, Ene reactions, Transmetalation, Diastereoselection.*

The intramolecular allylmetalation of double or triple bonds ('metallo-ene cyclization') offers an attractive stereocontrolled route to five- and six-membered carbo- and heterocyclic systems. Its application to the synthesis of many complex natural products over the past 15 years attests to the viability of this reaction type [1-5]. In addition to the existing stochiometric (Mg) and catalytic (Pd, Ni, Rh) procedures, we recently described a novel Pd-catalyzed Zn-ene reaction, that combines high diastereoselectivity and particular mildness with the possibility to trap the cyclized organozinc intermediates with a variety of electrophiles (*Scheme 1*) [6-8].

Scheme 1



Herein, we present the application of this protocol to the synthesis of (-)-erythrodiene (**1**), a marine sesquiterpenoid isolated from the Caribbean gorgonian octocoral *Erythropodium Caribaeorum* [9]. The rare spirobicyclo[4.5]decane skeleton of erythrodiene has attracted considerable synthetic effort over the past four years, but up to now efficient stereocontrol of

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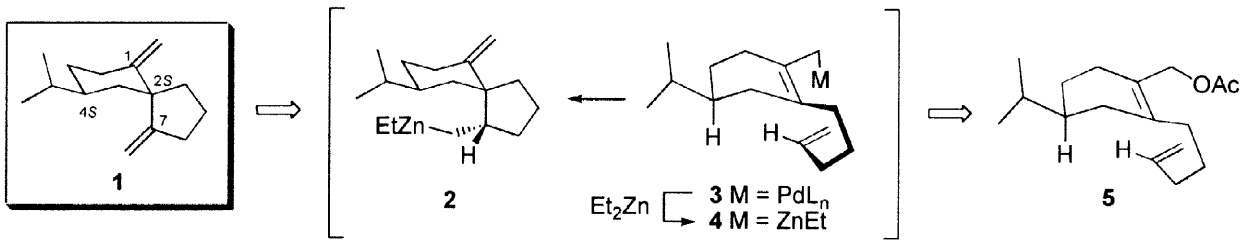
the spirocenter C2 remained an unsolved problem [10-14]. Therefore, we planned a new approach in which the spirocenter C2 would be formed *via* a Zn-ene cylization **3** → **2** (*Scheme 2*).

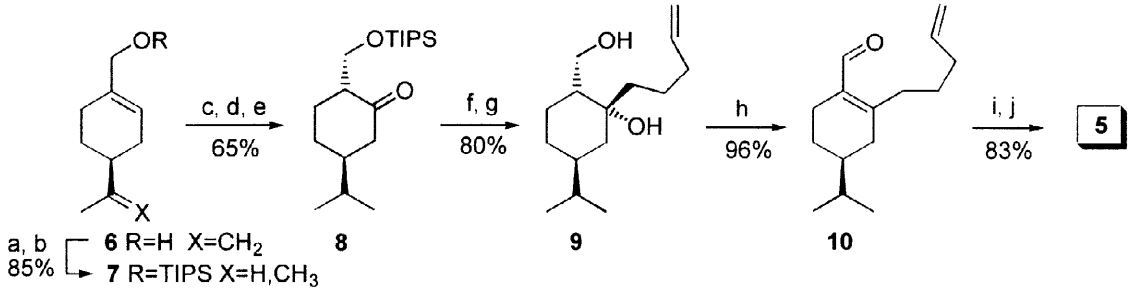
Scheme 2



Due to the well organized transition state of this reaction type, we expected that the *i*-Pr group at C4 would efficiently direct the cyclization to the opposite ring face in order to obtain the desired 2,4-*trans* diastereochemical relationship. The allylzinc intermediate **3** is formed from the Pd-allyl complex **4** *via in situ* transmetalation with excess Et_2Zn.

Acetate **5** was chosen as a suitable precursor for the formation of intermediate **4**. Its synthesis from the commercially available (-)-(*S*)-perillyl alcohol **6** is outlined in *Scheme 3*.[1]

Scheme 3



a) 0.2% PtO_2, H_2; b) TIPSCl, imidazole; c) BH_3•DMS, NaOH, H_2O_2; d) TPAP, NMO; e) K_2CO_3, MeOH; f) 5-Bromo-4-pentene, Mg; g) Bu_4NF; h) i. Py•SO_3, DMSO; ii. KOH, MeOH/H_2O; i) DIBAH; j) Ac_2O, Py.

After selective hydrogenation of the exocyclic double bond and hydroboration/oxidation of the endocyclic double bond, the resulting ketone **8** was isolated as a 1:1 mixture of diastereo-isomers. This is of no consequence as the stereogenic center will be lost during subsequent

[1] All new compounds were characterized with $[\alpha]_D$-values, IR, ^1H and ^{13}C-NMR, MS and elemental analysis and/or HRMS. Selected analytical data for acetate **5**: $[\alpha]^{22}_D$ = -71.4° (c = 0.9, $CHCl_3$). ^1H-NMR ($CDCl_3$, 400 MHz): 5.80 (*ddt*, *J*=17.3, 10.2, 6.6 Hz, 1H), 5.01 (br. *d*, *J*=17.3 Hz, 1H), 4.96 (br. *d*, *J*=10.2 Hz, 1H), 4.55 (AB, *J*=11.9 Hz, 2H), 2.17-1.96 (*m*, 7H), 2.05 (*s*, 3H), 1.85-1.73 (*m*, 2H), 1.52-1.41 (*m*, 3H), 1.34-1.23 (*m*, 1H), 1.16 (*qd*, *J*=11.9, 5.8 Hz, 1H), 0.90 (*d*, *J*=6.6 Hz, 6H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 171.4, 138.6, 137.6, 125.3, 114.6, 64.4, 40.3, 33.7, 33.6, 32.8, 32.2, 28.5, 28.1, 26.1, 21.1, 19.8, 19.7 .

transformations. However, in order to avoid working with mixtures, the crude ketone **8** was subjected to base-induced equilibration. From the resulting 5:1 diastereomeric mixture pure 1,4-*trans*-isomer was isolated in 65% yield by chromatography. The crystalline diol **9**, obtained diastereochemically pure after *Grignard* reaction, was converted into the α,β-unsaturated aldehyde **10** in a one-pot reaction sequence. Thus, the primary hydroxyl function was first oxidized using the *Parikh-Doering* protocol [15] and then regiospecific water elimination was effected by addition of a basic H_2O/MeOH solution. Reduction of aldehyde **10** and acetylation of the resulting allylic alcohol yielded the required acetoxydiene **5**.

After exposing **5** to an excess of Et_2Zn in the presence of $Pd(PPh_3)_4$ (5%) in Et_2O at 38°C for 14 h, the organozinc intermediates were quenched with iodine to yield iodide **12** in 52% yield, along with 15% of starting material and 15% of the reduced byproduct **11**, which presumably arises *via* protonation of the allylzinc intermediate **3** (*Scheme 4*).

Scheme 4

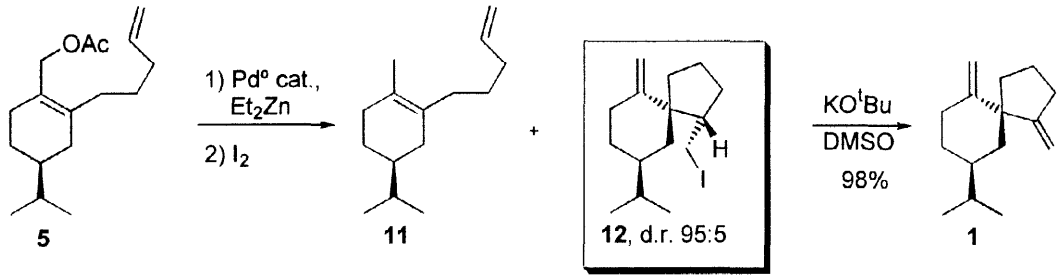


Table 1

Pd - catalyst	conversion[a)]	diene **11**	iodide **12** [b, c)]
$Pd(PPh_3)_4$ (5%)	80%	15%[b)]	52%
$Pd(OAc)_2$ / 1 equiv. Bu_3P (5%)	97%	3%[a)]	90%

a) GC-determined; b) isolated yields; c) d.r. 95:5 (by GC- and NMR- analysis).

In order to accelerate the formation of the Pd-allyl intermediate **4**, the $Pd(PPh_3)_4$ catalyst was replaced by a coordinatively unsaturated complex resulting from the reduction of $Pd(OAc)_2$ with one equivalent of Bu_3P according to *Tsuji and coworkers* [16].[1] This effected not only a

[1] In a typical experiment, a 0.02 N solution of $Pd(OAc)_2/Bu_3P$ 1:1 in degassed Et_2O (0.5 mL, 0.03 mmol, 5%) was added to the solution of acetate **5** (54 mg, 0.2 mmol) in 3 mL of Et_2O in a Carius tube. After dropwise addition of Et_2Zn (480 mg, 3.9 mmol, 20 equiv.) the tube was closed and warmed to 38°C with magnetic stirring for 14 h. After cooling to 25°C, the solution was quenched by dropwise addition of 1 N solution of I_2 in THF (8 mL). After dilution with pentane and washing with an aqueous NaS_2O_3 solution, the organic layer was concentrated and the residue purified by chromatography to yield 60 mg (90%) of iodide **12**. Selected analytical data for **12**: $[\alpha]^{21}_D$ = +7.3° (c=1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz): 4.78 (br. *s*, 1H), 4.63 (br. *s*, 1H), 3.15 ("*ddd*", *J*=9.4, 2.7, 1.5 Hz, 1H), 2.68 (*dd*, *J*=13.0, 3.3 Hz, 1H), 2.52-2.47 (*m*, 1H), 2.32 ("*dt*", *J*=13.0, 3.3 Hz, 1H), 2.04-1.93 (*m*, 3H), 1.88-1.70(*m*, 4H), 1.48-1.37 (*m*, 3H), 1.27-1.22 (*m*, 1H), 1.04 ("*qd*", *J*=12.5, 3.8 Hz, 1H), 0.86, 0.85 (2 *d*, *J*=6.4, 2·3H), 0.80 (*t*, *J*=12.6, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 152.1, 107.8, 53.7, 46.0, 41.7, 39.6, 35.2, 35.5, 32.4, 31.5, 29.4, 20.1, 19.6, 19.5, 14.0.

virtually complete conversion, but also suppressed the formation of byproducts and thus improved the isolated yield of iodide **12** to 90% (*Table 1*).

The diastereomeric ratio of 95:5 was constant in all experiments, confirming the expected sensibility of this mild cyclization reaction to the directing effect of the resident chiral center C4. The tentatively assigned *R*-configuration at C7 in iodide **12**, substantiated by NOE studies, is in accordance with the preferred *endo*-cyclization mode shown in *Scheme 2*. Finally, quantitative dehydroiodination from iodide **12** yielded a 95:5 diastereomeric mixture of dienes. After chromatography on $AgNO_3$-coated silica, diastereomerically pure (-)-erythrodiene (**1**) was obtained, which exhibited identical physical and spectroscopical properties to those reported for the natural product ($[\alpha]^{20}_D$ = -112°, $CHCl_3$, c = 0.6) [9].

In summary, we have achieved a highly diastereoselective synthesis of (-)-erythrodiene (**1**) in 11 steps and 24% overall yield from a commercially available precursor. We are currently working on the extension of this methodology on the intramolecular allylzincation of carbon-oxygen double bonds.

Acknowledgments

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