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Toward a Total Synthesis of an Aglycone of Spiramycin; Preparation of a C-10/C-15 Fragment

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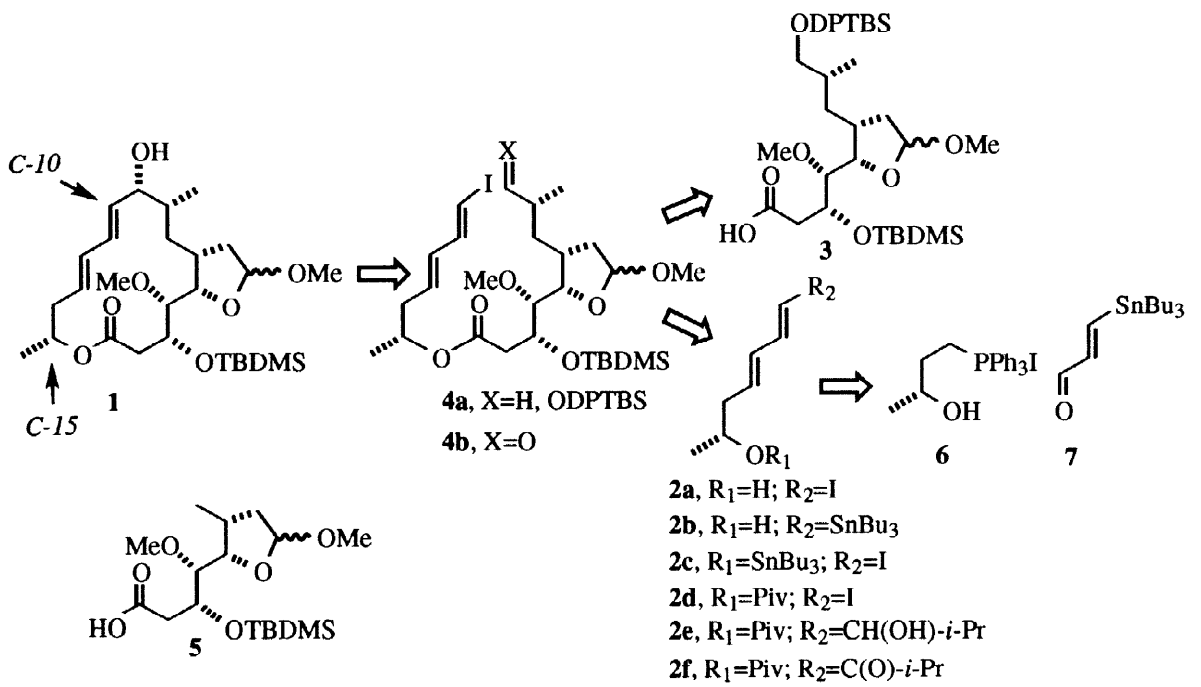
Abstract: *Esters of the dienyl iodide* ***2a****, which was obtained stereoselectively from the corresponding tin derivative* ***2b****, were shown to condense with* i*-butyraldehyde in the conditions of the Kishi-Nozaki-Takai reaction without alteration of the* E,E *configuration of the butadiene moiety.*

Pursuing our synthesis of the aglycone **1** of spyramycin, we turned our attention to the preparation of the iodide **2a** whose condensation with the acid **3**, followed by sequential deprotection and oxidation of the alcohol functionality at C-9 in the expected ester **4a** would furnish the iodoaldehyde **4b**, potentially convertible into the target aglycone **1** by a chromium-mediated Barbier condensation.[1]



Whereas a few examples of transition-metal-catalysed displacement of an iodine atom by a carbon residue in dienyl iodides related to **2a** have been reported without explicit reference to any *Z-E* isomerisation in the starting diene,[2] the simplest term, *i.e.* 1-iodo-1,3-butadiene, has proved to be sensitive, especially to light or traces of acid, the *E* stereomer isomerising partially in these conditions to give, at the equilibrium, a 2/3 mixture of the *E* and the *Z* isomer, respectively.[1c] Therefore, it was imperative to design a protocol permitting to obtain stereoselectively the iodide **2a** and, in the sequel, by using *inter alia* the model acid **5**,[3] to verify that the planned, ensuing, esterification and Kishi-Nozaki-Takai-coupling reactions could be performed without isomerisation of the *E,E* butadienyl system. Results along this line are reported herein, the completion of the synthesis of the aglycone **1** being disclosed in the accompanying Letter.

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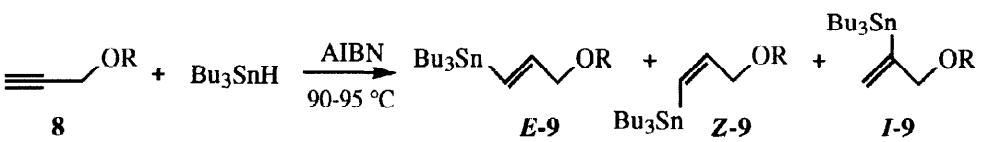
An obvious way to prepare the iodide **2a** was to perform a Wittig condensation of the phosphonium salt **6** with the stannylated aldehyde **7**, then to carry out a tin-iodine exchange in the resulting diene **2b**: a phosphonium salt related to **6** has been shown to react with excess base and aldehydes to give the corresponding, essentially pure, *E* olefins[4] and electrophilic-substitution reaction of vinyltin compounds with iodine is reputed to occur with retention of configuration of the starting carbon-carbon double bond.[5]

By modifying slightly a published procedure,[6a] the preparation of the aldehyde **7** was initiated by reacting the silyl derivative **8a** with excess Bu_3SnH in presence of AIBN at 90-95 °C (bath), what afforded a 8/1/1 mixture (NMR) of the isomeric stannyl compounds ***E*-9a**, ***Z*-9a** and ***I*-9a**, respectively (Table). Column chromatography (silica gel, 4/1 hexane/AcOEt) permitted then to isolate pure ***E*-9a** (62%), which afforded the aldehyde **7** (48% overall yield, from **8a**) by sequential treatment with TBAF and $BaMnO_4$ as described.[6a]

Since the tributylstannylation of the related propargyl compounds **8b** and **8c** has been shown to proceed under thermodynamic control at temperature higher than 80 °C, the *Z* adduct isomerising then to give the corresponding, more stable, *E* isomer,[6c] the O-DPTBOS (*i.e.* diphenyl-*t*-butoxysilyl) derivative **8d** was experimented in the above conditions with the hope that, due to the large size of the DPTBOS protecting-group, the less crowded (as compared to ***Z*-9d** and ***I*-9d**) adduct ***E*-9d** would form almost exclusively. For the sake of comparison, related experiments with the free alcohol **8b** and its O-THP derivative **8c** were reproduced (Table).[6d]

Table:



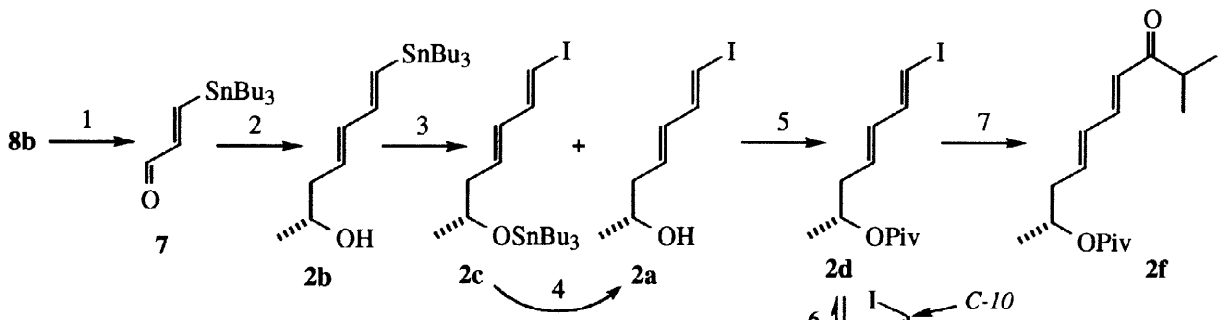
8 ***E*-9** ***Z*-9** ***I*-9**

Substrate	Composition of the crude product (%)		
	***E*-9**	***Z*-9**	***I*-9**
8a, R=TBDMS	80	10	10
8b, R=H	84	8	8
" *(from ref. 6c)*	88	5	7
8c, R=THP	74	15	11
8d, R=DPTBOS	80	10	10

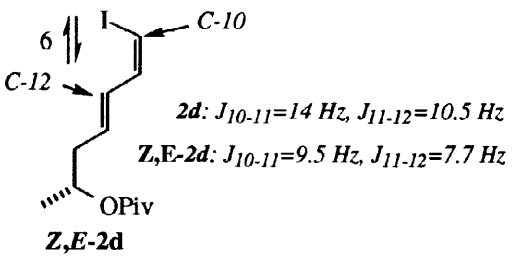
Contrary to our expectation, the best result was obtained by using the free alcohol **8b**. Noteworthy, separate treatment of a mixture of ***Z*-9d** and ***I*-9d** by Bu_3SnH and AIBN at 95 °C did not result in the formation of the isomer ***E*-9d**.[6e] In short, the preparation of **7** was realised on a larger scale (ca 10-20 g) by treating directly propargyl alcohol with excess Bu_3SnH and AIBN at 90-95 °C for a few hours, the crude reaction being then submitted to a high vacuum in order to eliminate excess reagent. Column chromatography of the residue gave the pure alcohol ***E*-9b** which was oxidised quantitatively by $BaMnO_4$ as above to give the aldehyde **7** (68% overall, from **8b**). Finally, condensation of **7** with the ylid generated by treating the enantiomerically-pure salt **6**[7] with excess LiHMDS in THF delivered the target diene **2b** with a fairly good selectivity (*E*,*E*>95%), as established by NMR.

Treatment of the stannylated diene **2b** by iodine in CH_2Cl_2 at 0°C in the dark resulted indeed in the formation of the iodide **2a**, but accompanied by its O-tributylstannyl derivative **2c**. Fortunately, treatment of **2c** by TBAF in THF gave cleanly additional iodide **2a**. The overall yield (from **2b**) in pure **2a** was reasonably good (62%).[8] Noteworthy, though it could be kept in the fridge (-30 °C) for a few weeks without noticeable alteration when diluted in hexane, *with added reduced-copper powder*, the iodide **2a**, as well as its O-derivatives (*vide infra*),

proved to be very sensitive at room temperature, especially when exposed to daylight, in which conditions the corresponding 1-*Z*,2-*E* isomer formed, as evidenced by ^{1}H NMR. Accordingly, *all operations* required by both the preparation of **2a** and its subsequent reactions were performed in protecting steadily any vessels from light.



Reagents and conditions: 1- *i*) Bu_3SnH (1.3 eq.), AIBN (0.04 eq.); 90-95 °C, 3 hours; *ii*) $BaMnO_4$ (8 eq.), CH_2Cl_2; r. t., 4 days; 2- **6** (1 eq.), LiHMDS (2.1 eq.), THF; r.t., 5 hours; 3- I_2 (excess), CH_2Cl_2; 0 °C, then excess KF, r. t., 2 hours; 4- TBAF.3 H_2O (excess), THF, then KF (excess); r.t., 2 hours (62% overall, from **6**); 5- pivaloyl chloride (1.5 eq.), pyridine (2 eq.), DMAP (0.12 eq.), CH_2Cl_2; 0 °C to r. t., 6 hours (98%); 6- neat or as a $CDCl_3$ solution; day light, a few hours; 7- $CrCl_2$ (4 eq.), $NiCl_2$ (0.04 eq.), DMSO; r. t., 2 hours (69%); DDQ (1.1 eq.), benzene; r. t., 12 hours (70%).



2d: $J_{10\text{-}11}$=14 Hz, $J_{11\text{-}12}$=10.5 Hz

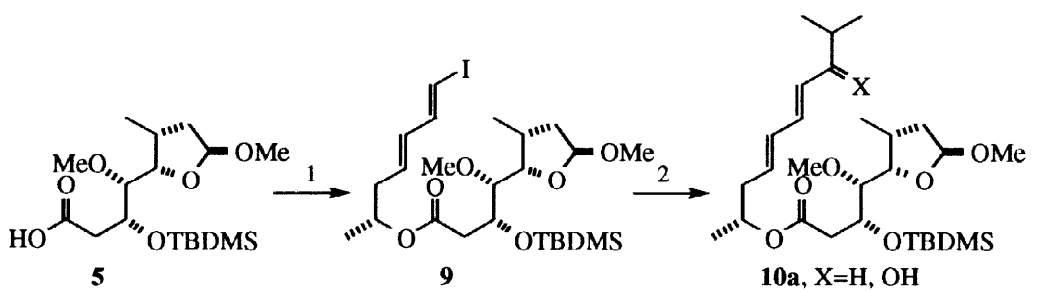
Z,E-2d: $J_{10\text{-}11}$=9.5 Hz, $J_{11\text{-}12}$=7.7 Hz

***Z,E*-2d**

The Kishi-Nozaki-Takai reaction of the ester **2d**, which was obtained with an excellent yield (98%) by treating **2a** with pivaloyl chloride and DMAP, was then explored by using *i*-butyraldehyde as model aldehyde.

Both the solvent and the composition of the reducing reagent proved crucial. Whereas no reaction was observed in THF, the coupling product **2e** formed smoothly in DMSO, provided the initial Ni(II)/Cr(II) ratio was not too low however.[9] Hence, slow addition of a mixture *i*-butyraldehyde and **2a** to a slurry of excess $CrCl_2$ and $NiCl_2$ (Ni/Cr=0.01) in DMSO, at room temperature, followed by chromatography, resulted in the isolation of the alcohol **2e** (69%) as a mixture of diastereomers (^{13}C NMR), which, by subsequent oxidation with DDQ, furnished the ketone **2f** (70%) .

Finally, condensation of **2a** with the acid **5** by using Yamaguchi conditions,[10] to form the ester **9**, followed by coupling of **9** with *i*-butyraldehyde (same conditions as above) and oxidation by DDQ of the resulting alcohol **10a** afforded the unsaturated ketone **10b**.[11]



Reagents and conditions: 1- *i*) NEt_3 (1.3 eq.), 2,4,6-trichlorobenzoyl chloride (1.2 eq.), THF; r. t., 1 hour, then filtration; *ii*) DMAP (6 eq.), **2a** (1.05 eq.), toluene; r. t., 4 hours (90%); 2- same conditions as for the **2d-2f** conversion (78x77%).

In conclusion, the preparation of the fragment C-10/C-15 (*i. e.* **2a**) of our planned synthesis of the aglycon **1** of spiramycin has been achieved and the conditions for connecting this synthon to the remaining part of the molecule has been contrived. Final assembling, leading to the aglycone **1**, is described in the accompanying letter.

Acknowledgement: Thanks are due to Rhône-Poulenc Rorer for a grant (to G. O.)

References and Notes

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2- Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138-2152.

3- Oddon, G.; Uguen, D.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 1149-1152.

4- Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 790-792.

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6- a) Wender, P. A.; McN.Sieburth, S.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967-3975; b) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265-2267; c) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851-3854. See, also: Lai, M.-T.; Li, D.; Oh, E.; Liu, H.-W. *J. Am. Chem. Soc.* **1993**, *15*, 1619-1628; d) The propargyl derivative, Bu_3SnH (1.3 eq.), and AIBN (0.04 eq.) were mixed in a Schlenk tube. After being perfectly degassed (freeze and thaw protocol), the mixture was heated at 90-95 °C for three hours in an argon atmosphere. Excess reagent was removed in vacuo and the residue was analysed by NMR; e) This result (the only one of our study of that stannation process to be at variance with Jung's observations)[6c] is consonant with an earlier report of the stability of related *E*-1- and *Z*-1-propenylstannane derivatives in similar conditions (Seyferth, D.; Vaughan, L. G. *J. of Organomet. Chem.* **1963**, *1*, 138-152).

7- Breuilles, P.; Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 6607-6610.

8- *Protocol for the **2b-2a** conversion*: A 0.14 M CH_2Cl_2 solution of iodine was added to a cooled (ca 0 °C) solution of the diene **2b** (2.75 mmol) in CH_2Cl_2 (15 ml) until the brown-red colour of iodine persisted. The resulting mixture was concentrated to ca 5 ml in vacuo and excess, finely grounded, KF was added. After being stirred for 2 h at room t. the mixture was filtered on a sintered glass-funnel and the filtrate was evaporated. The residue was chromatographed on silica gel (CH_2Cl_2) to give, after elution of a forerun fraction containing the stannyl derivative **2c**, the iodide **2a** (386 mg). The iodide **2c** was taken up in THF (5 ml) and TBAF (1 g) was added. The resulting solution was immediately concentrated in vacuo and excess KF was added. After 2 hours stirring the preceding filtration-evaporation-chromatography operations were applied to give additional **2a** (44.7 mg; total yield: 62%).

9- The condensation proceeded faster in DMF than in DMSO whatever the Ni(II)/Cr(II) ratio was, but, for unknown reasons, the yield in alcohol **2d** did not exceed 40% by using DMF as solvent.

10- Inanaga, J.; Hirata, K.; Sacki, T.; Katsuki, M., Yamaguchi, M. *Bull. Chem. Soc. Jpn* **1979**, *52*, 1989-1993.

11- Selected data: **2a**: ^1H NMR: 1.2 (d, J=6.2 Hz, 3H), 2.1-2.25 (m, 2H), 3.75-3.9 (m, 1H), 5.65-5.8 (dt, J=15.2, 7.6 Hz, 1H), 6.06 (dd, J=15.2, 10.4 Hz, 1H), 6.25 (d, J=14.4 Hz, 1H), 7.01 (dd, J=14.4, 10.4 Hz, 1H); ^{13}C NMR: 23.05, 42.34, 67.18, 78.24, 131.51, 133.2, 145.08; **2f**: ^1H NMR: 1.05-1.35 (m, 18H), 2.42 (t, J=6.3 Hz, 2H), 2.81 (hept, J=6.9 Hz, 1H), 4.97 (sext, J=6.2 Hz, 1H), 6-6.3 (m, 3H), 7.16 (dd, J=15.4, 10 Hz, 1H); ^{13}C NMR: 18.56, 19.57, 27.19, 38.8, 39, 39.51, 69.2, 127.06, 131.73, 139.41, 142.14, 178.01, 204.32; UV: λ_{max}=273nm (ε=16300, MeOH); **9**: ^1H NMR: -0.06, (s, 3H), 0.09 (s, 3H), 0.86 (s, 9H), 1.01 (d, J=7Hz, 3H), 1.22 (d, J=6.2 Hz, 3H), 1.7-2 (m, 2H), 2.25-2.8 (m, 4H), 3.14 (dd, J=4.1, 1.5 Hz, 1H), 3.36 (s, 3H), 3.42 (s, 3H), 4.32 (dd, J=7.1, 1.1 Hz, 1H), 4.45-4.54 (m, 1H), 4.95 (sext, J=6.3 Hz, 1H), 5.04 (d, J=4.9 Hz, 1H), 5.65 (td, J=15, 7.3 Hz, 1H), 6.01 (dd, J=15, 10.5 Hz, 1H), 6.21 (d, J=14.3 Hz, 1H), 6.98 (dd, J=14.3, 10.5, 1H); ^{13}C NMR: -4.62, -4.53, 15.35, 18.05, 19.75, 25.87, 34.23, 38.39, 39.02, 40.95, 54.93, 57.61, 67.48, 69.78, 77.3, 77.6, 81.12, 104.62, 130.51, 133.03, 145.11, 172.59; **10b**: ^1H NMR: 0.05 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 1 (d, J=7, 3H), 1.1-1.15 (m, 6H), 1.23 (d, J=6.3 Hz, 3H), 1.65-2 (m, 2H), 2.4-2.9 (m, 6H), 3.13 (dd, J=4.3, 1.9 Hz, 1H), 3.34 (s, 3H), 3.4 (s, 3H), 4.32 (dd, J=7.3, 1.6 Hz, 1H), 4.41-4.5 (m, 1H), 4.95-5.11 (m, 2H), 6-6.3 (m, 3H), 7.15 (dd, J=15.4, 10 Hz, 1H); ^{13}C NMR: -4.62, -4.56, 15.32, 18.03, 18.55, 19.82, 25.85, 34.2, 34.96, 38.34, 39.54, 40.92, 54.88, 57.56, 67.43, 69.65, 77.02, 81.11, 104.62, 127.13, 131.68, 139.34, 142.13, 172.57, 204.2; UV: λ_{max}=263nm (ε=22900, MeOH); $[\alpha]_D^{21}$ +71 (c=0.6, CH_2Cl_2). The ^1H and ^{13}C NMR spectra were recorded at 200 and 50 Mhz, respectively, on $CDCl_3$ solutions.