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An Allylic Isoprenoid C_5 Nucleophile for the Synthesis of Forskolin

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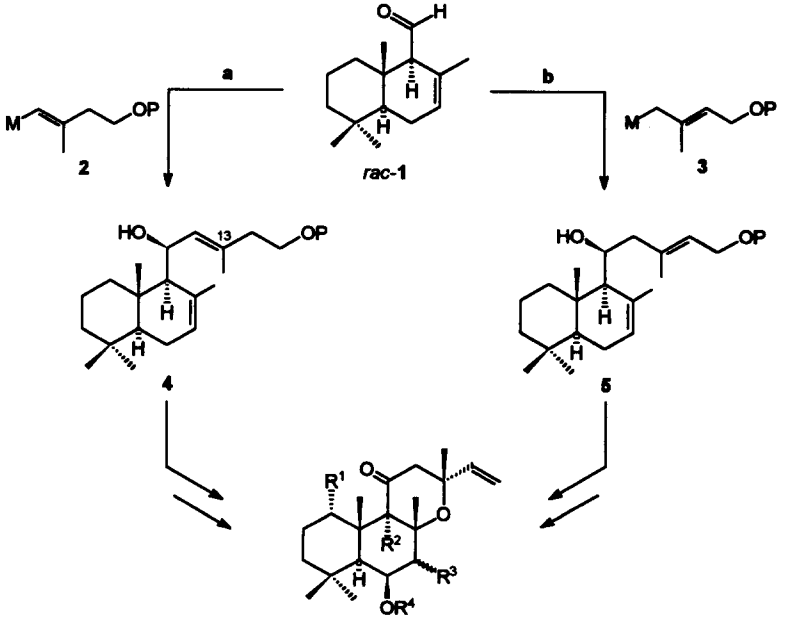
Abstract - $InCl_3$-mediated coupling of δ-alkoxy allylic stannane **9b** with aldehydes has been shown to give the α-coupling products in high yield, probably via two S_E' processes. Most specifically, drimenal (*rac*-**1**) has been converted into labdane derivative **17** which is considered to be an important intermediate on the way to forskolin. © 1997 Published by Elsevier Science Ltd.

Forskolin (**6c**) is a labdane diterpene that has been shown to interact with different membrane proteins including adenylyl cyclase, the glucose transporter, the voltage-gated potassium channel, and ligand-gated ion channels.[1] The ability of forskolin to stimulate adenylyl cyclase in intact cells in the absence of hormonal agonists has been exploited by many laboratories for investigation of the role of cyclic AMP in various physiological functions. The mode of binding to the adenylyl cyclase has been studied in detail.[2]



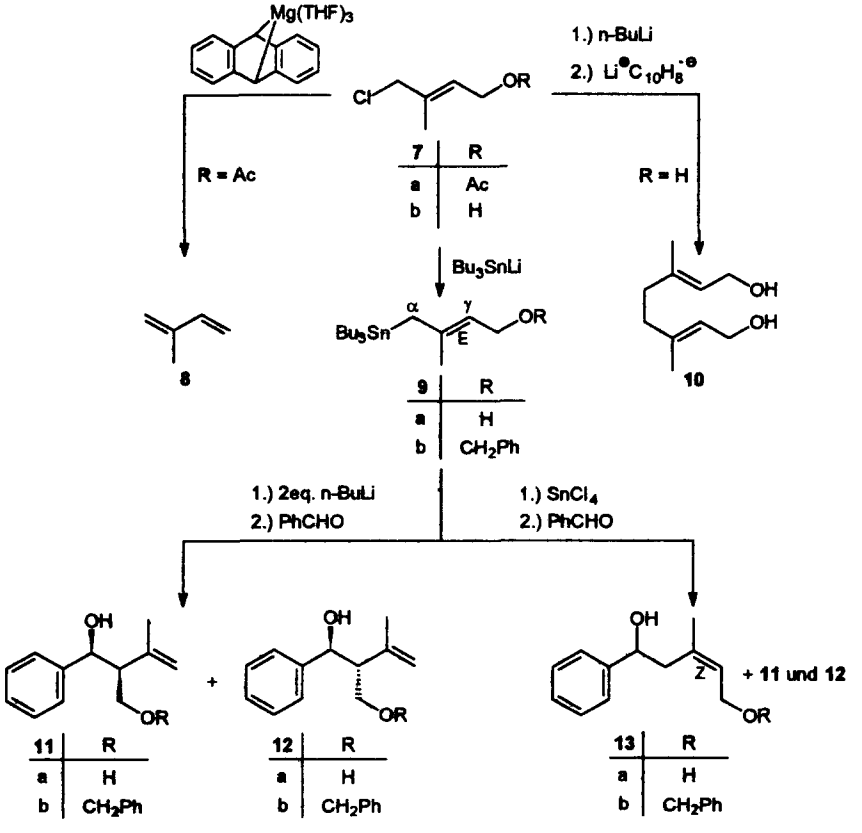
6	R^1	R^2	R^3	R^4
a	H	H	α-I	Ac
b	H	H	β-OAc	H
c	OH	OH	β-OAc	H

P = protecting group

Forskolin has been the subject of massive synthetic efforts.[3] In contrast to practically all other synthetic approaches we have devised a synthetic plan (via **6a** and the 1,9-dideoxy derivative **6b**) that is based entirely on isoprenoid building blocks.[4] On the way to **6a** the vinyllithium reagent **2** was coupled to racemic drimenal (*rac*-**1**, obtained from (E,E)-farnesol) to furnish the labdane derivative *rac*-**4**. The oxygen functionality at C-13 was then introduced by a diastereoselective Sharpless I epoxidation.[5]

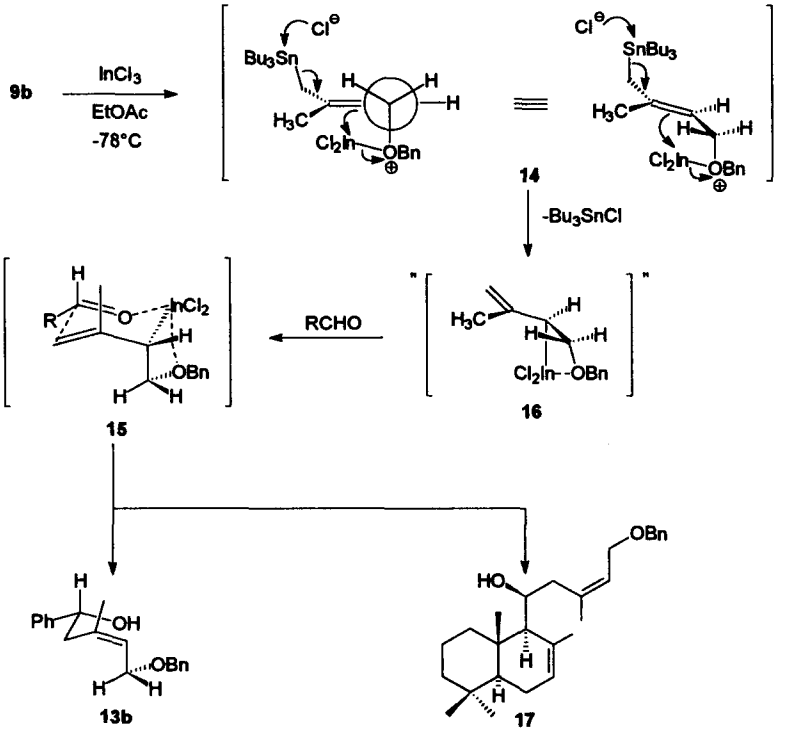
From the beginning we were more interested to use an allylic nucleophilic reagent of type **3**[6] instead of **2** to prepare *rac*-**5**, because we expected to have then the option of introducing the 13-oxygen functional group by a Kazuki-Sharpless epoxidation[7] and thus perform a kinetic resolution at this step.[8] Exploratory attempts along these lines met with failure and we were only able to use approach *b* with umpoled reagents, at the expense of several functional group interconversions.[8]

It is the purpose of the present Communication to describe experiments which led eventually to the development of a procedure allowing to perform the reaction *rac*-**1** + **3**, as desired.



In previous experiments it was impossible to couple **7a** with drimenal (*rac*-**1**) via a Grignard reagent even when the reaction was performed at -78°C using the highly active magnesium powder obtained from magnesium anthracene.[9] The only product obtained from **7a** was isoprene.[8] Guided by work of Seebach,[10] Barluenga,[11] and Kessler[12] we then converted **7b** (obtained from **7a** by hydrolysis with $Ba(OH)_2$ in methanol[13]) into its alkoxide on reaction with n-BuLi in THF and treated this with 2 equivalents of lithium naphthalenide at -100°C to provide the dianion. Then benzaldehyde was added. In contrast to results obtained with 2-lithioalkoxides which

could be trapped with electrophiles,[10,11,12] the only product formed from **7b** was the Wurtz coupling product **10** (66%). In order to avoid this unwanted reaction, **7b** was converted into the allyl stannane **9a** on treatment with tributylstannyl lithium (in THF solution at -78°C). After conversion of **9a** into the dianion with n-butyllithium (2 equiv.) and subsequent trapping with benzaldehyde the desired C-C bond formation was observed, however with allylic inversion. A mixture of the racemic diastereoisomers **11a** and **12a** was obtained in 55% yield. It is known that the problem of allylic inversion can be overcome by a sequence of two S_E' reactions.[14,15] When, for example an allyl stannane is treated with a Lewis acid such as $SnCl_4$ and subsequently with the aldehyde it is assumed that a reactive trichlorostannane intermediate is formed with the $SnCl_3$ substituent in the γ position which then reacts with the aldehyde under a second allylic inversion. Under these conditions **13a** was obtained in 25% yield from **9a** and benzaldehyde. The configuration at the double bond was determined by NMR spectroscopy ($\delta(CH_3)$ = 24.27, NOE between the methyl and the olefinic proton) and found to be (Z) as expected from the mechanistic rationale of Thomas.[15] Besides **13a** the γ-products **11a** and **12a** were obtained (40%). When the same sequence of reaction was performed starting from **9b** the overall yield was higher (82%) but again the γ-products (**11b** and **12b**) were formed in excess.



Recently, Marshall has demonstrated that this type of chemistry with α-oxygenated allylic stannanes profits from the use of $InCl_3$ as Lewis acid.[16] We were interested whether similar improvements could be established with δ-alkoxy allylic stannanes such as **9b**. Thus, $InCl_3$ was sonicated in ethyl acetate and to this solution (0.04 mol/l) benzaldehyde (1 equiv.) was added. Then at -78°C the allylic stannane **9b** (1.5 equiv.) was added and the mixture was allowed to warm to ambient temperature. After work-up **13b** was isolated in 98% yield. Under the

same conditions from **9b** and drimenal (*rac*-**1**) labdane **17** was obtained in 66% yield, probably via **16** and the cyclic transition state **15**.[15] The configuration around the side chain double bond was (Z) as shown by ^{13}C NMR ($\delta(CH_3) > 20$).[17]

In conclusion, a major improvement has been achieved for the conversion of a drimane to a labdane derivative on the way to forskolin.

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REFERENCES AND NOTES

1 For leading references and studies on the interaction of forskolin on P-glycoprotein, see Morris, D.I.; Greenberger, L.M.; Bruggemann, E.P.; Cardarelli, C.; Gottesman, M.M.; Pastan, I.; Seamon, K.B. *Mol.Pharmacol.* **1994**, *46*, 329-337.

2 Zhang, G.; Liu, Y.; Ruoho, A.E.; Hurley, J.H. *Nature* **1997**, *386*, 247-253, and references therein.

3 For leading references, see Anies, C.; Pancrazi, A.; Lallemand, J.-Y. *Bull.Soc.Chim.Fr.* **1997**, *134*, 183-202; Anies, C.; Pancrazi, A.; Lallemand, J.-Y.; Prangé T. *ibid.* **1997**, *134*, 203-222.; Liu, H.-J.; Shang, X. *Heterocyles* **1997**, *44*, 143-147.

4 Zimmermann, S.; Bick, S.; Welzel, P.; Meuer, H.; Sheldrick, W.S. *Tetrahedron* **1995**, *51*, 2947-2952, and previous papers on this subject.

5 See Narula, A.S. *Tetrahedron Lett.* **1982**, *23*, 5579-5582, and references therein.

6 Cf. Depew, K.M.; Danishefsky, S.J.; Rosen, N.; Sepp-Lorenzino, L. *J.Am.Chem.Soc.* **1996**, *118*, 12463-12464.

7 For leading references, see McKee, B.H.; Kalantar, T.H.; Sharpless, K.B. *J.Org.Chem.* **1991**, *56*, 6966-6968.

8 See Jordine, G.; Bick, S.; Möller, U.; Welzel, P.; Daucher, B.; Maas, G. *Tetrahedron* **1994**, *50*, 139-160.

9 Aleandri, L.E.; Bogdanovic', B. in Fürstner, A. (ed.), *Active Metals*, VCH, Weinheim 1995, p. 299-338.

10 Nájera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289-300.

11 Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc. Perkin Trans. 1* **1983**, 3019-3026; Barluenga, J.; Fernández-Simon, J.L.; Concellón, J.M.; Yus, M. *J. Chem. Soc. Perkin Trans. 1* **1988**, 3339-3343.

12 Wittmann, V.; Kessler, H. *Angew. Chem.* **1993**, *105*, 1138-1140; *Angew.Chem.Int.Ed.Engl.* **1993**, *32*, 1091.

13 Ohsugi, M.; Takahashi, S.; Ichimoto, I.; Ueda, H. *Nippon Nogei Kagaku Kaishi* **1973**, *47*, 807-811, *C.A.* **1974**, *81*, 3280z.

14 Review: Marshall, J.A. *Chem.Rev.***1996**, *96*, 31-47.

15 Review: Carey, J.S.; Coulter, T.S.; Hallett, D.J.; Maguire, R.J.; McNeill, A.H.; Stanway, S.J.; Teerawutgulrag, A.; Thomas, E.J. *Pure Appl.Chem.* **1996**, *68*, 707-710.

16 Marshall, J.A.; Hinkle K.W. *J.Org.Chem.* **1996**, *61*, 105-108.

17 ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87, 0.90, 0.96 (3 s, 9H, CH_3-18, CH_3-19, CH_3-20), 1.07-1.22 (3H), 1.39-1.63 (4H), 1.80-1.98 (10H), 1.84 and 1.88 (2s, CH_3-16 and CH_3-17,) 2.03/2.81 (AB of ABX, $J_{12a/12b}$ = 13.4 Hz, $J_{12a/11}$ = 4.0 Hz, $J_{12b/11}$ = 10.1 Hz, CH_2-12), 3.96-4.09 (11-H), 3.98 (d, $J_{15/14}$ = 7.0 Hz, CH_2-15), 4.49/4.54 (AB, J_{AB} =11.7 Hz, $OC\underline{H}_2Ph$), 5.58-5.67 (7-H, 14-H), 7.30-7.36 (Ar-H).- ^{13}C NMR (50.3 MHz, $CDCl_3$, APT): δ = 14.79 (-), 19.28 (+), 22.71 (-), 23.93 (+), 24.51 (-), 25.15 (-), 33.37 (+), 33.86 (-), 37.58 (+), 40.52 (+), 42.63 (+), 42.98 (+), 50.53 (-) (C-5), 60.32 (-) (C-9), 66.52 (+) (C-15), 67.61 (-) (C-11), 72.88 (+) ($O\underline{C}H_2Ph$), 124.56 (-)/126.57 (-) (C-7/C-14), 128.11 (-) (Ar-C), 128.39 (-) (Ar-C), 128.86 (-) (Ar-C), 132.92 (+)/139.80 (+) (C-13/C-8), 138.63 (+) (Ar-C-ipso).

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