Diastereoselective Pentadienylation Reaction of Protected Chiral α-Amino Aldehydes

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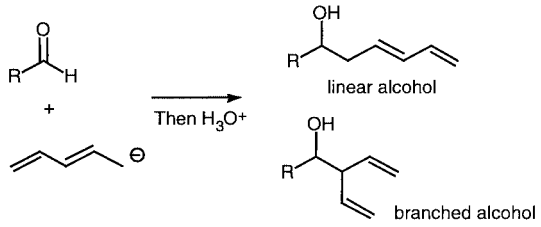
Abstract: Diastereoselective pentadienylation of chiral α-amino aldehydes was achieved. The obtained *anti* amino alcohols can be transformed into dienic imines which undergo Diels-Alder cyclisation to give stereoselectively indolizidines.

Key words: chiral α-amino aldehydes, pentadienylation, Diels-Alder reaction, indolizidines

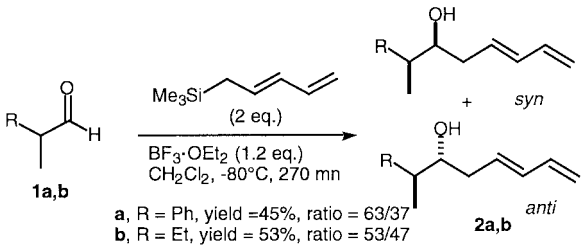
The allylation reaction of aldehydes has been widely studied and is recognized as a powerful route to functionalized alcohols. Many diastereoselective examples of this reaction have been described.[1] In contrast, the reaction of pentadienyl anions with aldehydes has been much less investigated. These reactions can give two types of products (Scheme 1). As early as 1965,[2] Miginiac et al. reported that the reaction of pentadienyllithium with aldehydes leads to mixtures of linear and branched alcohols, whereas the corresponding zinc reagent regioselectively gives the branched alcohol. More recently, it has been reported that treatment of 5-bromo-1,3-pentadiene with indium metal in the presence of an aldehyde or a ketone results in the formation of a branched alcohol.[3] On the other hand, pentadienylsilanes and stannanes are known to lead exclusively to the linear product.[4,5] Such linear dienols can be further elaborated for use in the synthesis of natural products, in particular using the introduced diene in a Diels-Alder or hetero-Diels-Alder reaction.[6]



Scheme 1

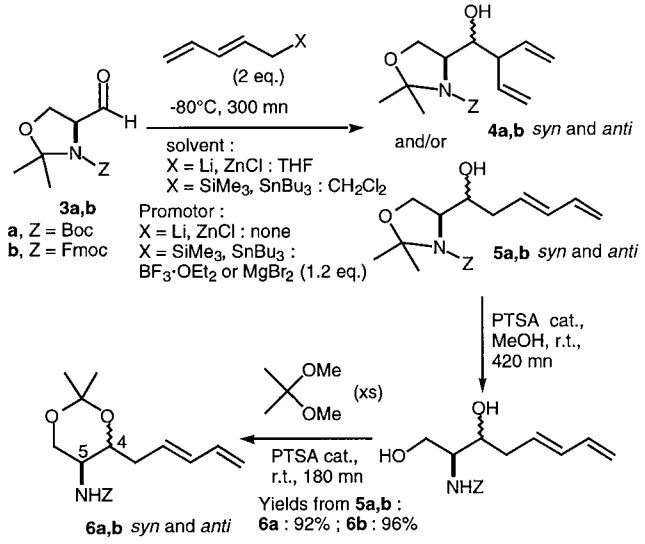
To the best of our knowledge, nothing is known about the stereoselectivity of pentadienylation reactions leading to linear alcohols.[7] In this note, we present our first results about the reaction of pentadienyl anion equivalents with α-chiral aldehydes, especially protected serinals. An application of this strategy to the stereoselective synthesis of indolizidines is also reported.

First experiments were run with pentadienylsilane and the simple aldehydes **1a**,**b** (Scheme 2). As expected, only the linear alcohols **2a**,**b** were isolated. However the observed stereoselectivity (**a** :63/37; **b** :53/47)[8] was poor and no effort was made to determine the relative configuration of the major isomers.



Scheme 2

More interesting were the results obtained with the two serinal analogues **3a**,**b** (Scheme 3). Representative results are summarized in the Table.



Scheme 3

When pentadienyllithium[9] was reacted with aldehyde **3a** (Garner's aldehyde,[10] entry 1), a mixture of branched and linear alcohols was obtained. These compounds can be

easily separated by liquid chromatography. However, we were not able to determine the *syn*/*anti* ration directly for the isolated alcohols **5**. They were transformed in two steps[11] into the dioxanes **6** for which this ratio can be readily obtain by HPLC. Furthermore, the *syn* and *anti* isomers of **6a**,**b** can be separated by preparative liquid chromatography. The stereochemistry of the major and minor isomers were determined by ^{1}H NMR.[12] The reactions with pentadienylzinc chloride (entries 2,7) gave regioselectively the branched alcohols **4a**,**b**. No attempt at determining the *syn*/*anti* ratio of these branched alcohols was made. On the other hand, pentadienyltrimethylsilane and pentadienyltributylstannane led exclusively to the linear alcohols **5a**,**b**. As in the case of allylation reactions, a promoter had to be used in order to activate the used aldehyde in these reactions. For the corresponding allylation reactions, monodentate activators, such as BF_3, lead to the formation of the *anti* isomer as the major product, whereas the use of bidentate Lewis acids, such as $MgBr_2$, gives mainly the *syn* isomer.[1] As seen from the table (for instance entries 3 and 5), the stereoselectivity of the pentadienylation reaction is independent of the used Lewis acid (at least for boron and magnesium). In every cases, the *anti* isomer dominates, with a *anti*/*syn* ratio around 9/1, the only exeption being entry 10 in which the ratio is closer to 4/1.

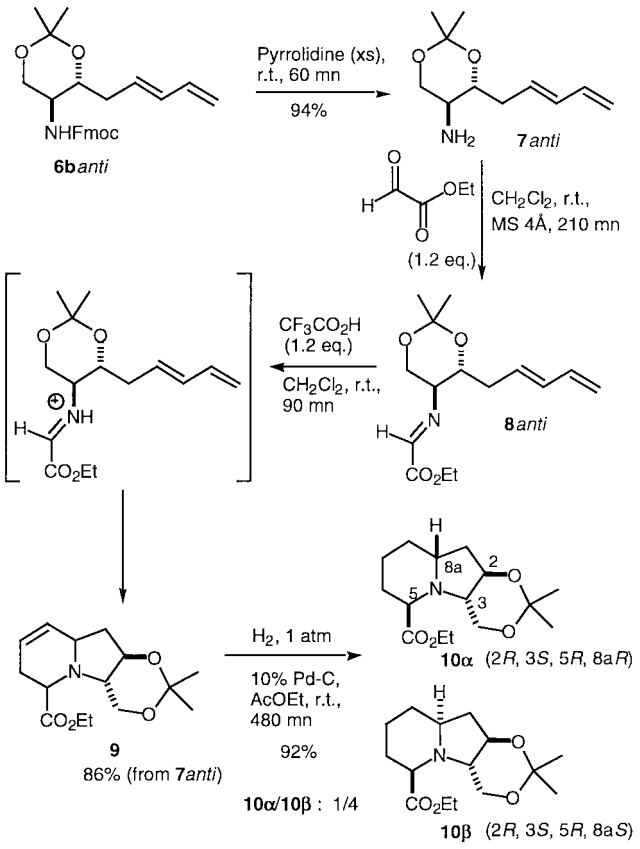
Table Synthesis of compounds **4**, **5** and **6**

Entry	Z	X	Promoter	yield (%) **4+5**	ratio **4/5**	**6***anti*/ **6***syn*
1	Boc	Li	none	80	47/53	91/9
2		ZnCl	none	92	100/0	
3		$SnBu_3$	$BF_3{\cdot}OEt_2$	74	0/100	91/9
4		$SiMe_3$	$BF_3{\cdot}OEt_2$	84	0/100	90/10
5		$SnBu_3$	$MgBr_2{\cdot}OEt_2$	72	0/100	88/12
6		$SiMe_3$	$MgBr_2{\cdot}OEt_2$	64	0/100	88/12
7	Fmoc	ZnCl	none	74	100/0	
8		$SnBu_3$	$BF_3{\cdot}OEt_2$	75	0/100	92/8
9		$SiMe_3$	$BF_3{\cdot}OEt_2$	82	0/100	88/12
10		$SnBu_3$	$MgBr_2{\cdot}OEt_2$	73	0/100	79/21
11		$SiMe_3$	$MgBr_2{\cdot}OEt_2$	76	0/100	88/12

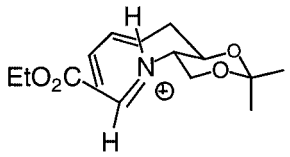
The *anti* selectivity observed in the case of BF_3-promoted reactions can be adequately explained using a simple Felkin-Anh model as in the case of allylation reactions.[1] However, we have no precise rational for the *anti* selectivity obtained using $MgBr_2$. We think that it might be due to a late transition state, closer to the final products than in the case of allylation reactions. If this is the case, even though it is probably kinetically controlled,[1] the *anti*/*syn* ratio will largely reflect the relative stability of these isomers.

In order to demonstrate that the alcohols **5** are interesting synthons, we studied their use in a hetero-Diels-Alder reaction.[13] The amine **7***anti* was obtained by deprotection of **6b***anti* (Scheme 4).[14] Treatment of **7***anti* with ethyl glyoxylate gave the imine **8***anti* which was relatively stable[15] and did not undergo a spontaneous [4π+2π] cyclisation. However, when treated with trifluoroacetic acid, **8***anti* readily cyclized, via the corresponding iminium, and gave the tricyclic compound **9**. This heterocycle was obtained as a mixture of isomers which we were not able to separate. Hydrogenation of **9** gave the indolizidine **10** as a mixture of two isomers (ratio 4/1). These isomers were separated by liquid chromatography and careful examination of their NMR spectra[16] shows that the major isomer **10β** has a (2*R*, 3*S*, 5*R*, 8a*S*) configuration whereas the minor isomer **10α** has a (2*R*, 3*S*, 5*R*, 8a*R*) configuration. Formation of the major isomer **10β** would result from an attack of the iminium onto the *Re*-face of the diene, as depicted in the Figure. The configuration of carbon 5 seems to indicate an *endo* attack; however, we cannot exclude a possible epimerization of this stereogenic center after the Diels-Alder reaction.

10α and **10β** are precursors for various natural indolizidines.[17] We are presently studying their chemistry.



Scheme 4



Figure

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References and Notes

(1) For a review, see : Fleming, I. In *Comprehensive Organic Synthesis*, vol. 2; Trost, B. M. and Fleming, I., Eds; Heathcock, C. H., vol. Ed.; Pergamon Press: Cambridge, 1991; p. 563.

(2) Miginiac-Croizeleau, L.; Miginiac, P.; Prévost, C. *Bull. Soc. Chim. Fr.* **1965**, 3560. Gérard, F.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1974**, 1924.

(3) Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573.

(4) Seyferth, D.; Pornet, J. *J. Org. Chem.* **1980**, *45*, 1721. Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 3783. Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K. *Chem. Lett.* **1983**, 1683.

(5) Beryllium derivatives : Yasuda, H.; Ohnuma, Y.; Nakamura, A.; Kai, Y.; Yasuoka, N.; Kasai, N. *Bull. Chem. Soc. Jpn* **1980**, *53*, 1101.

(6) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240. Ainsworth, P. J.; Craig, D.; Reader, J. C.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1996**, *52*, 695.

(7) Use of a chiral pentadienyl borane leading to a branched alcohol : Sugimone, M.; Yamamoto, Y.; Fujii, K.; Ito, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9608.

(8) Ratio determined by HPLC. Column : Nucleosil Siμ 250 x 4.6; eluant : cyclohexane/isopropanol: 99.6/0.4.

(9) Bates, R. B.; Gosselink, D. W.; Kaczynski, J. A. *Tetrahedron Lett.* **1967**, 199.

(10) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18. **3b** was prepared in a similar way. Full desciption of this new serinal analogue will be reported elsewhere.

(11) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354. Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979. Tchertchian, S.; Vallée, Y. *Tetrahedron* **1998**, *54*, 7777.

(12) The coupling constant J_{H4H5} is characteristic of the configuration : J_{H4H5} = 1-2 Hz for *syn* dioxanes, whereas J_{H4H5} = 7-10 Hz for *anti* dioxanes. [11] For **6b**, major isomer : J_{H4H5} = 9.5 Hz (*anti*); minor isomer : J_{H4H5} = 1.5 Hz (*syn*). Attributions were confirmed by NOE experiments.

(13) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. Waldmann, H. *Synthesis* **1994**, 535. Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707. Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 635 and references therein.

(14) Carpino, L. A.; Han, G. Y. *J. Am. Chem. Soc.* **1970**, *92*, 5748; *J. Org. Chem.* **1972**, *37*, 3404.

(15) In the ^{1}H NMR spectrum, the proton of the HC=N group was observed as a singlet at 7.73 ppm (300 MHz, $CDCl_3$).

(16) All new compounds gave spectroscopic and analytical data in agreement with the assigned structures.
10β: $[\alpha]_D^{20}$+5.5 (c 0.8, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) 0.93 (t, 3H, *J* = 7.1Hz, CH_3 ester), 1.01-1.06 (m, 2H, 7-H and 8-H), 1.27-1.32 (m, 2H, 1-H and 8-H), 1.36 (s, 3H, CH_3 dioxane), 1.43-1.48 (m, 2H, 6-H and 7-H), 1.56 (s, 3H, CH_3 dioxane), 1.60-1.67 (m, 1H, 6-H), 2.13-2.20 (m, 1H, 1-H), 3.00-3.10 (m, 2H, 3-H and 8a-H), 3.44 (dd, 1H, *J* = 11.4 and 2.8Hz, 5-H), 3.74-3.95 (m, 4H, CH_2 ester, 2-H and one H of CH_2O), 4.18 (dd, 1H, *J* = 10.0 and 3.9Hz, one H of CH_2O); ^{13}C NMR ($CDCl_3$, 75MHz) 14.14 (CH_3 ester), 19.71 (CH_3 dioxane), 21.65 (6-C), 23.72 (7-C), 29.51 (CH_3 dioxane), 29.67 (8-C), 34.75 (1-C), 54.74 (3-C), 58.11 (8a-C), 60.05 (5-C), 61.02 (CH_2 ester), 66.62 (CH_2 dioxane), 74.67 (2-C), 100.10 (C dioxane), 172.14 (C = O).
10α: $[\alpha]_D^{20}$+55.8 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500MHz) 1.16-1.23 (m, 1H, 8β-H), 1.25 (t, 3H, *J* = 7.1Hz, CH_3 ester), 1.31-1.46 (m, 2H, 1α-H and 7β-H), 1.38 (s included in preceeding m, 3H, CH_3 dioxane), 1.47 (s, 3H, CH_3 dioxane), 1.78-1.87 (m, 2H, 1β-H and 6β-H), 1.88-1.98 (m, 2H, 7α-H and 8α-H), 2.10-2.19 (m, 1H, 6α-H), 2.62 (ddd, 1H, *J* = 12.0, 8.9 and 4.5Hz, 3-H), 3.00-3.06 (m, 1H, 8a-H), 3.58 (ddd, 1H, *J* = 12.0, 8.6 and 4.1Hz, 2-H), 3.67 (dd, 1H, *J* = 8.9 and 2.1Hz, 5-H), 3.72 (t, 1H, *J* = 10.8Hz, 1H of CH_2O), 3.92 (dd, 1H, *J* = 10.8 and 4.5Hz, 1H of CH_2O), 4.08-4.18 (m, 2H, CH_2 ester); ^{13}C NMR ($CDCl_3$, 75MHz) 14.30 (CH_3 ester), 19.29 (CH_3 dioxane), 27.68 (6-C), 29.21 (7-C), 29.56 (8-C), 29.60 (CH_3 dioxane), 29.95 (1-C), 58.12 (8a-C), 59.50 (3-C), 60.00 (5-C), 60.28 (CH_2 ester), 63.13 (CH_2 dioxane), 72.40 (2-C), 98.88 (C dioxane), 173.33 (C=O). Attribution of relative configurations were made using one and two dimensional NOE experiments in $CDCl_3$ and C_6D_6.

(17) Michael, J. P. *Nat. Prod. Rep.* **1997**, 619. Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137.

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