Ene Approach for Concurrent Control over the Chiral Centres at C-20 and C-22 of Steroid Side Chains: a Highly Stereocontrolled Synthesis of (20*S*,22*R*)-(*erythro*-)22-Hydroxy-23,24-acetylenic Steroid Side Chains

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The ene reactions of a (*Z*)-$\Delta^{17(20)}$-steroidal olefin with acetylenic aldehydes in the presence of Me_2AlCl produce (20*S*,22*R*)-(*erythro*)-22-hydroxy-23,24-acetylenic steroid side chains with high diastereoselectivity and diastereofacial selectivity.

Recently considerable attention has been focused on the development of methodologies for the stereocontrolled synthesis of steroid side chains, particularly the 22*R*/α-hydroxy side chains that appear in the brassinosteroids (plant-growth-promoting substances).[1,2] Unfortunately, however, the conventional route *via* the reaction of a steroidal (20*S*)-22-aldehyde with a metal acetylide produces mixtures of Cram (22*R*/α) and anti-Cram (22*S*/β) isomers with low diastereofacial selectivity.[1—3]† We now report a new ene approach for concurrent control over the chiral centres at C-20 and C-22 of steroid side chains,‡ in which ene reactions of a steroidal olefin (**1**) with acetylenic aldehydes (**2**) in the presence of Me_2AlCl[5] provide (20*S*,22*R*)- (*erythro*-) (brassinolide-type) side chains (**3**) [reaction (i)].

The reaction of the easily obtainable olefin (**1**)[7] with 3-trimethylsilylprop-2-ynal (**2b**) is representative. To a dry solution in CH_2Cl_2 (5 ml) of the olefin (**1**) (1 mmol, 0.444 g) and the aldehyde (**2b**) (1.1 mmol, 0.048 g) was added a solution of Me_2AlCl (1.1 mmol) in hexane (1.1 ml) at −78 °C. The usual work-up with ($NaHCO_3$) followed by silica gel column chromatography gave the (20*S*,22*R*)-(*erythro*-) alco-

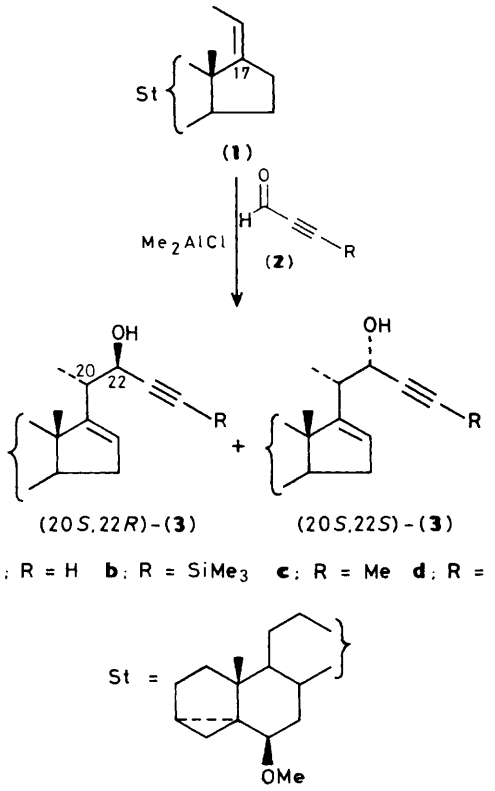
Table 1. Ene reactions of the steroidal olefin (**1**) with aldehydes (**2**).[a]

Entry	Aldehyde	Combined yield (%)[b]	22*R*/α : 22*S*/β[c]
1	(**2a**)	0	
2	(**2b**)	Quant.	>95 :<5
3	(**2c**)	90	90 : 10
4	(**2d**)	Quant.	90[d]: 10
5[e]	(**2d**)	80	90 : 10

[a] All reactions were carried out on a 1 mmol scale under argon with Me_2AlCl unless otherwise noted. [b] Yield of isolated product after silica gel chromatography. [c] The isomer ratio was determined by 500 MHz ^1H n.m.r. and/or t.l.c. analysis. [d] The (22*R*)-(**3c**) was isolated pure after silica gel chromatography, in 78% yield. [e] 2,6-Di-t-butyl-4-methylphenoxy(methyl)aluminium chloride was used instead of Me_2AlCl.

† Recently, titanium tetrachloride-mediated alkynylation with stannylacetylenes was found to produce the Cram isomer with high diastereofacial selectivity.[3]

‡ The ability of the α-face ene reaction to set the stereochemistry of C-20 in the natural 20*S*-configuration has been reported.[4] There is no report, however, of concurrent control over the chiral centres at C-20 and C-22 *via* the ene reaction.

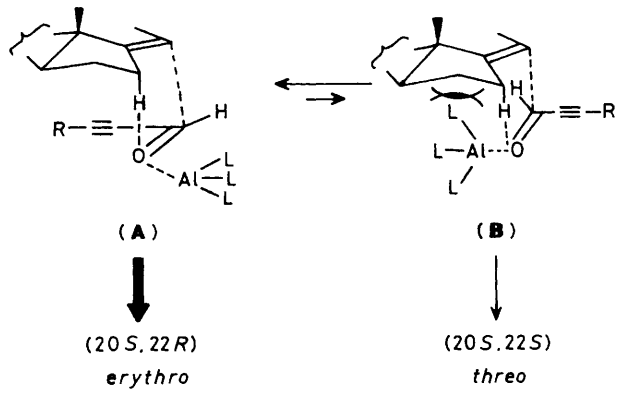


hol (**3b**)§ as a single stereoisomer in quantitative yield, without decomposition of the acid-labile cyclic ether system.

All the ene reactions studied except for that with propynal (**2a**)¶ afforded good yields of the ene products (Table 1). Surprisingly enough, high (20*S*,22*R*)- (*erythro*-) selectivities (at least *ca.* 9 : 1) were observed (entries 2—5).‖

The stereochemical assignments of the ene products (**3**) deserve comment. The (20*S*,22*R*)- (*erythro*-) configuration of (**3b**) was confirmed after conversion into (**3a**) (Bu^n_4NF, aq. THF) through comparison with authentic (20*S*,22*R*)-(*erythro*-) and (20*S*,22*S*)- (*threo*-) (**3a**)[6] by ^1H n.m.r. and t.l.c. analysis.** The stereochemical assignments of the ene products (**3c**) and (**d**) were based on comparison (t.l.c. and ^1H n.m.r. data) with compound (**3a**).[6]**

Particularly noteworthy is the remarkably high *erythro*-selectivity observed.‖ Any mechanism for *erythro*-selectivity must be initiated by the complexation of the aldehyde with the



Lewis acid Me_2AlCl. Since the Lewis acid is complexed *anti* to the alkynyl group of the aldehyde,[10] we suggest that the α-face ene reaction proceeds preferentially *via* the *endo*-transition state (**A**), since the *exo*-conformer (**B**) would suffers a larger steric repulsion of the trivalent aluminium species by the cyclopentene ring.††

In conclusion, this work has demonstrated the utility of the new ene strategy as an efficient and highly stereoselective entry, with concurrent control over the chiral centres at C-20 and C-22, to (22*R*)-hydroxy-23,24-acetylenic steroid side chains from easily available steroidal olefins. The ene products will doubtless serve as key intermediates for the synthesis of many important side-chain-modified steroids; *e.g.* (22*R*)-(**3b**) and -(**3d**) could serve as key intermediates for brassinosteroids.[2] Work along these lines is under way.

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§ Recently we have reported the use of the [2,3] Wittig approach for concurrent control.[6] The [2,3] Wittig shift to give (**3d**), however, exhibited low diastereoselectivity (*erythro* : *threo* 1 : 1).

¶ An ene reaction involving a C≡C bond as an enophile followed by further ene reactions involving C=C and/or C=O bonds may occur with the terminally unsaturated acetylenic aldehyde (**2a**). Ene reactions involving C–C double or triple bonds as enophiles have been well documented for acrylaldehyde, vinyl ketones, propiolate, and acrylate.[8]

‖ To the best of our knowledge, there is no report of a Lewis-acid-mediated intermolecular ene reaction showing high *erythro* selectivity except for one case with chloral, where *ca.* 90% *erythro* selectivity was observed.[9] We found that the ene reaction of (**2b**) with 2-methyl but-2-ene exhibited *ca.* 90% erythro selectivity.

** Definitive distinguishing features are the 16- and 22-H signals and the t.l.c. R_f values.

†† The use of the 2,6-di-t-butyl-4-methylphenoxy(methyl)aluminum chloride was found, however, to result in almost the same diastereoselectivity, with a decrease in yield of the ene adduct (**3d**).