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4,5-*erythro*/5,6-*threo*-Stereoselectivity in vinylogous Mukaiyama aldol addition of a silyloxypyrrole to a threose derivative: stereochemical rationalization and relevance to (+)-castanospermine synthesis

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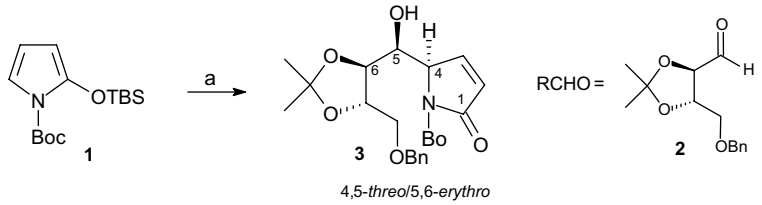
Abstract—Vinylogous Mukaiyama aldol addition of *N*-*p*-methoxybenzyl-4-methoxy-2-trimethylsilyloxypyrrole **7** to bis-MOM threose **6** using $SnCl_4$ as promoter gave the 4,5-*erythro*/5,6-*threo* adduct **8**, with the correct absolute configurations for the castanospermine framework as determined by a single-crystal X-ray structure. A transition-state model is presented to rationalize the stereoselectivity.

Lewis-acid promoted vinylogous Mukaiyama aldol reactions using silyloxypyrroles have developed into a powerful asymmetric methodology for rapid access to a variety of natural-product skeletons[1] including those of alkaloids.[2] Of note is the seminal work carried out by Casiraghi's group, who have elegantly demonstrated the application of *N*-Boc-2-(*tert*-butyldimethylsilyloxy)pyrrole (TBSOP) **1** to asymmetric synthesis.[3] In the case of a substrate-controlled addition to a chiral aldehyde such as Mukaiyama's acetonide[4] **2** (see Scheme 1), four possible diastereomeric products are possible, and Casiraghi et al. has demonstrated[5] that the 4,5-*threo*/5,6-*erythro* product **3** can be selectively accessed in high yield by reaction of **1** with **2** using $SnCl_4$ as a promoter, Scheme 1. Similarly, reaction between **1** and *O*-isopropylidene-D-glyceraldehyde using $BF_3{\cdot}OEt_2$ as promoter reversed the 4,5-diastereoselectivity to afford the corresponding 4,5-*erythro*/5,6-*erythro* adduct.[6]

To date there is no efficient method for accessing the other two diastereomers. In particular, realization of the 4,5-*erythro*/5,6-*threo* stereomotif (or 7,8-*threo*/8,8a-*erythro* using castanospermine numbering) would provide rapid accesss to the framework of the potently bioactive indolizidine[7] alkaloid (+)-castanospermine;[8] indeed such a convergent approach has eluded several workers,[5,9] Figure 1.

We have recently reported[10] the application of *N*-benzyl-5-allyl-4-methoxy-2-trimethylsilyloxypyrrole to synthesize the lepadiformine tricyclic core, and it seemed attractive to us to investigate the application of the



Scheme 1. Reagents and conditions: (a) RCHO, $SnCl_4$ (1.2 equiv), ether, −85 °C.

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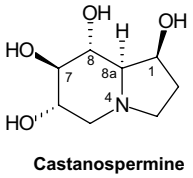
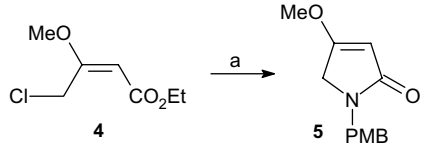


Figure 1. Structure of (+)-castanospermine.

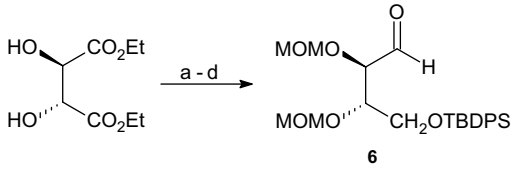
deallylated analogue to access the appropriate stereomotif of the castanospermine core. Of particular interest was the potential influence of the C-4 methoxy group on the diastereoselectivity of the vinylogous Mukaiyama[11] reaction as well as providing a functional-group platform for castanospermine C-1 hydroxyl group installation. In this Letter, we report on this chemistry as providing a solution to constructing the castanospermine indolizine precursor with correct configurations at carbons **8** and **8a**.

The pyrrolinone precursor **5** to our silyloxypyrrole was readily available by condensing benzylamine or *p*-methoxybenzylamine with commercially available enoate ester **4**, according to a known procedure.[12] In our hands, adding Hünig's base to the condensation reaction helped us to improve yields. Compound **4** was also available in a one-step reaction[12] from ethyl 4-chloroacetoacetate, Scheme 2.

For the tartrate-derived threose derivative, we decided to make changes to the acetonide **2** used extensively by



Scheme 2. Reagents and conditions: (a) *p*-methoxybenzylamine, EtN(*i*-Pr)$_2$, CH_3CN, Δ, (67%).



Scheme 3. Reagents and conditions: (a) P_2O_5, $(MeO)_2CH_2$, CH_2Cl_2, (96%); (b) $LiAlH_4$, THF, −20 °C, (78%); (c) (i) *n*-BuLi (1.1 equiv), THF, 0 °C; (ii) TBDPSCl (94% for two steps); (d) Swern oxidation (92%).

Mukaiyama and Casiraghi in their work, in order to probe stereoselectivity aspects. Thus, the acetonide protecting group was replaced by two MOM groups, which were introduced using P_2O_5 and dimethoxymethane. The benzyl group was also changed to TBDPS for chemoselectivity reasons. Scheme 3 depicts the four-step sequence to afford aldehyde **6**.

In keeping with our work on lepadiformine, we decided to use the one-pot-strategy for preparing the silyloxypyrrole involving the TMS dienol silyl ether rather than the TBS version used by Casiraghi. Thus, pyrrolinone **5** was treated with *n*-BuLi (1.5 equiv) at −78 °C for 30 min to generate the dienolate, which was silylated in situ with excess TMSCl (3 equiv) to generate silyloxypyrrole **7**. Thereafter, aldehyde **6** was added followed by $SnCl_4$ (2 equiv) and the reaction allowed to warm to −20 °C over a number of hours before being quenched, Scheme 4. Rapid stirring of the final reaction solution at low temperature was found to be crucial for producing a good result that avoided aggregation. To our delight, chromatographic purification furnished a major product **8**[13] in around 60–65% isolated yield (over several runs) that was crystalline. NMR spectroscopy revealed it to

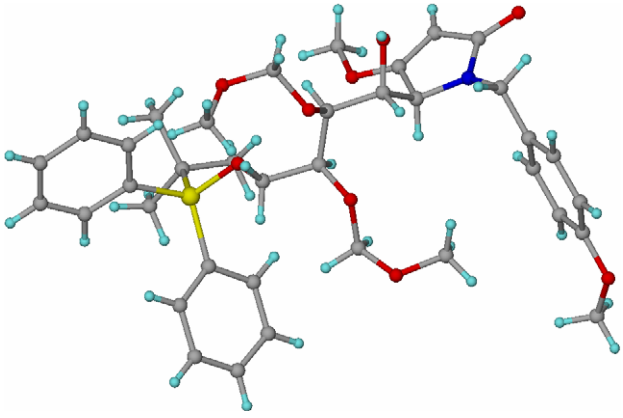


Figure 2. X-ray crystal structure[15] of **8**.

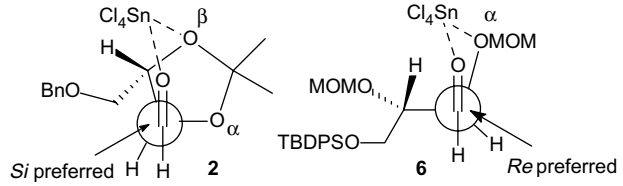
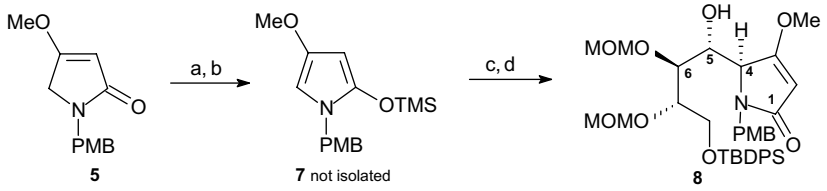


Figure 3. Facial selectivities for aldehydes **2** and **6**.



Scheme 4. Reagents and conditions: (a) *n*-BuLi (1.5 equiv), THF, −78 °C; (b) TMSCl (3 equiv), −78 °C; (c) aldehyde (0.7 equiv) **6**, −78 °C; (d) $SnCl_4$ (2 equiv), −78 °C to −20 °C (60–65% overall based on the aldehyde).

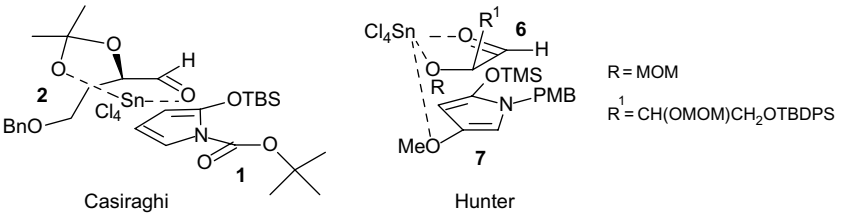


Figure 4. Transition-state models for formation of adducts **3** and **8**.

be a single diastereomer, with the H-4/H-5 coupling constant (see Scheme 1 for numbering) being around 2 Hz indicating[14] *erythro* relative stereochemistry in contrast to the *threo*-stereochemistry obtained by Casiraghi for **3** (Scheme 1). In order to establish the absolute stereochemistry, a single crystal X-ray determination[15] was carried out to reveal 4*S*,5*R*-configurations for **8** and, importantly, to establish four of the contiguous chiral centres for (+)-castanospermine, Figure 2.

Analysis of facial selectivities for producing Casiraghi's adduct **3** and our adduct **8** reveal the following. Overall, the reaction proceeds via ald (*Si*)/pyr (*Si*) for **3** versus ald (*Re*)/pyr (*Si*) for **8**. The aldehyde facial selectivities may be rationalized using a Felkin–Anh chelate for both, except that acetonide **2** used by Casiraghi (see Scheme 1) uses a β-chelate as proposed by Mukaiyama,[4] whereas our case involving **6** (Scheme 3) proceeds via an α-chelate.[16] Figure 3 summarizes these features.

Facial selectivities[14,17] on the two different silyloxypyrroles **1** and **7** are both *Si* but for different reasons. In Casiraghi's case, the aldehyde carbonyl group of **2** points more towards the *N*-Boc end where a possible cooperative interaction between tin and the carbamate carbonyl oxygen may play a role[18] in the transition state. Such an arrangement also ensures that the aldehyde chain points away from the pyrrole ring. Conversely, in our case, *Si*-face selectivity in **7** is consistent with the carbonyl group of aldehyde **6** pointing inwards over the pyrrole in an *endo*-Diels–Alder-like fashion,[17] to ensure that the C1–C2 bond of aldehyde **6** points away from the pyrrole ring to accommodate the C2 hydrogen. Furthermore, the C-4 methoxy group of **7** may possibly develop cooperative interactions with tin as shown in Figure 4, which suggests transition-state models for the two reactions.

In summary, this work provides a solution for the 4,5-*erythro*/5,6-*threo*-selectivity in silyloxypyrrole vinylogous Mukaiyama aldol additions pertaining to castanospermine synthesis. Studies directed at attempting to transform our 4,5-*erythro*-adduct to castanospermine will be reported in due course as well as the generality of using silyloxypyrrole **7** in this new stereoselective reaction.

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13. Data for adduct **8** (see Scheme 4 for numbering): Mp 107–108 °C (from ethyl acetate–hexane); $[\alpha]_D$ +6.67 (*c* 3.0, CH_2Cl_2); Found: C, 65.52; H, 7.36; N, 2.10. $C_{37}H_{49}NO_9Si$ requires C, 65.37; H, 7.26; N, 2.06; ν_{max} 3053 (OH), 2933 (CH), 1678 (C=O), 1628 (C=C) cm^{-1}; δ_H ($CDCl_3$, 300 MHz) 1.06 (9H, s, *t*-Bu), 3.08 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.75–3.90 (3H, m, H-7, H-8), 3.99 (1H, dd, *J* 7.0, 1.8 Hz, H-6), 4.08 (1H, d, *J* 2.0 Hz, H-4), 4.08 (1H, d, *J* 15.3 Hz, Bn), 4.19 (1H, dd, *J* 7.0, 2.0 Hz H-5), 4.22 (1H, d,

J 6.5 Hz, OCH_2O), 4.34 (1H, d, *J* 6.5 Hz, OCH_2O), 4.68 (2H, s, OCH_2O) 5.10 (1H, d, *J* 15.3, Bn), 5.20 (1H, s, H-3), 6.79 (2H, d, *J* 8.7 Hz, PMB), 7.17 (2H, d, *J* 8.7 Hz, PMB), 7.30–7.50 (6H, m, Ar), 7.60–7.70 (4H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 19.2 (Si–C), 26.8 ($(CH_3)_3$), 42.8 (CH_2), 55.2 (OCH_3), 55.5 (OCH_3), 56.3 (OCH_3), 58.1 (OCH_3), 60.9 (C-4), 62.4 (C-8), 68.3 (C-5), 77.9 (C-7), 80.9 (C-6), 95.7 (C-2), 96.8 (OCH_2O), 99.2 (OCH_2O), 114.0 (PMB), 127.7, 127.8, 129.2, 129.8, 129.9, 130.0, 133.0, 133.1, 135.4, 135.5 (Ar), 158.9 (PMB), 171.9 (C-3), 173.3 (C-1); *m*/*z* FAB: 702.2 $(M+Na)^+$, 680.3 $(M+H)^+$.

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15. CCDC 632910 contains the Supplementary Crystallographic Data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. $C_{37}H_{49}NO_9Si$ MW = 679.86 g mol^{-1}; colourless needle; crystal system: orthorhombic, space group $P2_12_12_1$, $a = 8.2069(1)$ Å, $b = 15.7691(1)$ Å, $c = 27.8258(3)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 3601.09(6)$ Å^3, $Z = 4$, calcd = 1.254 g cm^{-3}, $T = 153(2)$ K, = 0.120 mm^{-1}, $F(000) = 1\ 456$, $2.93° < 2 < 27.51°$, $(Mo_k) = 0.71073$ Å, crystal size $0.3 \times 0.2 \times 0.2$ mm^3; X-ray intensity data were collected with a Nonius KappaCCD diffractometer, 8224 unique reflections were collected of which 6882 were refined [$I > 2(I)$], $R_{int} = 0.0393$; the structure was solved by direct methods (SHELXS-97) and refined on F^2 using full-matrix least-squares procedures (SHELXL-97) giving $R_1 = 0.0415$ [$I > 2(I)$], $wR_2 = 0.1009$ (all data), GOF = 1.051, max/min residual electron density = 0.544/−0.387 eÅ^{-3}.
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