Asymmetric Conjugate Addition of Crotylstannane: Synthesis of (–)-Lasiol

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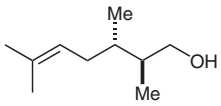
Dedicated to Professor David R. Williams, on the occasion of his 60th birthday

Abstract: Lasiol, the major component of the mandibular gland secretion, serves as the primary sex attractant of the male ant, *Lasius meridionalis*. Our interest in lasiol stems from the stereochemistry of the chiral methyl substituents and the synthetic challenges posed by this common structural motif. As such, an asymmetric 1,4-conjugate addition of an allylic stannane to produce the 1,2-*anti*-dimethyl arrangement with high stereocontrol has resulted in the synthesis of (–)-lasiol.

Key words: asymmetric synthesis, 1,4-addition, (–)-lasiol, chiral auxiliaries, Lewis acids

In 1990, lasiol (**1**, Figure 1) was isolated and identified by Jones and co-workers[1] as a mandibular gland secretion of the male ant *Lasius meridionalis*. Its structure, specifically, the *anti* relationship of the vicinal methyl stereocenters was determined by a combination of synthesis and spectroscopic techniques. The groups of Mori[2] and Kuwahara[3] later elucidated the absolute stereochemistry via synthesis of both enantiomers.



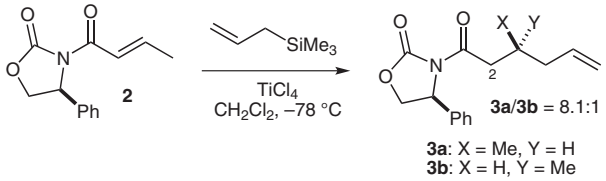
(–)-lasiol (**1**)

Figure 1

Owing to the difficulty posed by synthesis of the adjacent methyl stereogenic centers, several groups have undertaken and reported the synthesis of lasiol utilizing a variety of creative strategies.[4–6] Notable amongst these approaches are the application of a silyloxy-Cope rearrangement by Schneider,[7] the asymmetric allylic alkylation–cross metathesis–conjugate addition protocol by Feringa[8] and the stereoselective conjugate addition of a chiral enolate by Tadano.[9]

The use of 1,3-oxazolidinones as chiral auxiliaries is well known and has been widely exploited for imparting high levels of stereocontrol in a variety of C–C bond-forming reactions.[10] Nonracemic *N*-enoyl-1,3-oxazolidinones have found substantial utility in natural product synthesis,[11] particularly in providing for the highly diastereoselective conjugate addition reactions of organocopper species.[12] Pioneered in the Hruby laboratory,[13] nonracemic 4-phenyl-1,3-oxazolidinone has been especially productive as a chiral auxiliary in these reactions.

In 1992, Wu and co-workers[14] developed the $TiCl_4$-mediated conjugate addition reaction of allyltrimethylsilane to **2**, resulting in a reported 8.1:1 ratio of diastereomers **3a** and **3b** (Equation 1). These data were consistent with the mode of selectivity achieved in the extensive organocopper studies by Hruby and Williams. More recently, Koert and Gesson have exploited the $TiCl_4$-promoted conjugate addition of an allylsilane toward the synthesis of laulimalide analogues.[15] The stereochemistry obtained in their reaction was reported to converge with the results initially reported by Wu.



Equation 1 Conjugate addition reported by Wu and co-workers

In 2003, seeking to exploit the heightened reactivity of allylic stannanes as compared to allylic silanes, Williams and Mullins[16] described the asymmetric conjugate addition of allyl- and crotylstannanes to Lewis acid precomplexed nonracemic α,β-unsaturated *N*-enoyl-1,3-oxazolidinones. These studies revealed a curious reversal in stereochemical outcome when compared to the well-known conjugate addition of organocopper reagents to these same systems.[17] Perhaps more interestingly, these results ran contrary to those reported by Wu and co-workers in the conjugate addition of allyltrimethylsilane. Via a thorough reevaluation of Wu's reaction and comparison of the characteristic ^1H NMR absorption pattern of the diastereotopic C-2 methylene obtained in all three conjugate addition reactions (allyltrimethylsilane, allyltributyltin and allylcopper), Williams and Mullins corrected the stereochemical assignment of Wu, while conclusively establishing the convergence of the silane and stannane results. It was clearly demonstrated that, under both sets of conditions, the silane and stannane additions proceed with selectivity opposite to that of the analogous organocopper reagents (instead favoring **3b**).[18] In order to further clarify and bring attention to the stereochemical course of these conjugate addition reactions, as well as to demonstrate the

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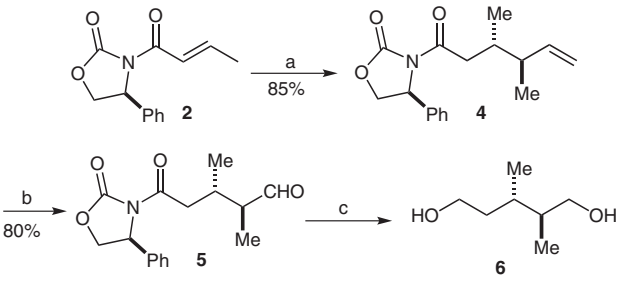
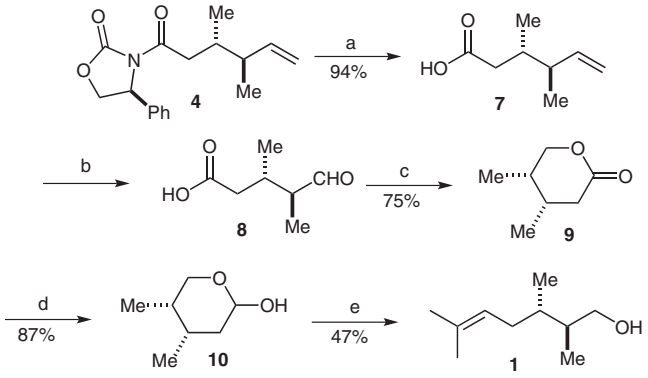
utility of this reaction for the stereoselective introduction of adjacent methyl stereogenic centers, we report herein our synthesis of (–)-lasiol.

As illustrated in Scheme 1, our synthesis begins with the conjugate addition to enoyloxazolidinone **2**. Precomplexation between **2** and zirconium tetrachloride is followed by addition of (*E*)-crotyl-tri-*n*-butylstannane to provide **4** with good facial selectivity (10:1).[19] Notably, this addition occurs with complete allylic transposition of the allylic stannane, resulting in the selective formation of the two vicinal stereogenic centers of lasiol in a single reaction. At this point, ozonolysis of the alkene was to be followed by reduction of the resulting aldehyde **5**, with the hope that spontaneous cyclization and extrusion of the chiral auxiliary would occur to give the lactone product. Unfortunately, our attempts to selectively reduce the aldehyde resulted in overreduction to give diol **6**. Although unexpected, these results can be rationalized by internal delivery of hydride to the imide carbonyl via the alkoxide which results from aldehyde reduction.



Scheme 1 *Reagents and conditions*: (a) (*E*)-crotyl-tri-*n*-butylstannane, $ZrCl_4$, CH_2Cl_2, –78 to –20 °C; (b) O_3, CH_2Cl_2, –78 °C, then Ph_3P; (c) $NaBH_4$, EtOH, 0 °C.

Given this result, our scheme was modified as shown in Scheme 2. Hydrolysis of **4** resulted in acid **7**, which was subjected to ozonolysis conditions to provide aldehyde **8**. Aldehyde **8** was immediately reduced and, upon quenching and stirring in the presence of H_2SO_4, spontaneous cyclization of the resulting alcohol occurred to provide lactone **9**. Reduction of the lactone was accomplished using diisobutylaluminum hydride to yield lactol **10** as an inconsequential mixture of diastereomers. Finally, treatment of the lactol mixture with an excess of $Ph_3P{=}C(CH_3)_2$[20] resulted in the formation of (–)-lasiol (**1**), the spectral data of which was identical to that reported previously.[9]



Scheme 2 *Reagents and conditions*: (a) LiOH, H_2O_2, THF–H_2O (1:1); (b) O_3, CH_2Cl_2, –78 °C, then Ph_3P; (c) $NaBH_4$, aq THF, then H_2SO_4; (d) DIBAL-H, CH_2Cl_2, –78 °C; (e) $Ph_3P{=}C(CH_3)_2$, THF, –78 to 0 °C.

In conclusion, a concise, stereoselective synthesis of (–)-lasiol has been completed. Utilizing the asymmetric conjugate addition of crotylstannane, the challenging 1,2-*anti*-dimethyl stereoarray has been assembled in a single transformation. Efforts toward the development of a rationale for the interesting reversal in facial selectivity observed in these conjugate addition reactions are ongoing.

Synthesis of 4

Zirconium tetrachloride (3.5 g, 15 mmol) was added in one portion to a solution of enoyloxazolidinone **2** (2.3 g, 10 mmol) in dry CH_2Cl_2 (100 mL) at –78 °C. The mixture was left to stir at –78 °C for 30 min, at which point (*E*)-crotyl-tri-*n*-butylstannane (6.9 g, 20 mmol) was introduced dropwise over 10 min. The reaction mixture was slowly warmed from –78 to –20 °C and left to stir at this temperature for 16 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ and allowed to warm to r.t. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes → hexanes–EtOAc = 6:1) to afford 2.4 g (85%) of **4** as a white solid; R_f = 0.41 (hexanes–EtOAc = 4:1); mp 74–76 °C. FTIR (thin film): 3069, 2965, 1782, 1706 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 5 H), 5.74–5.64 (m, 1 H), 5.36 (dd, *J* = 8.9, 3.6 Hz, 1 H), 4.94–4.85 (m, 2 H), 4.61 (t, *J* = 8.9 Hz, 1 H), 4.12 (dd, *J* = 8.9, 3.6 Hz, 1 H), 3.00 (A of ABX, J_{AB} = 16.0 Hz, J_{AX} = 5.3 Hz, 1 H), 2.84 (B of ABX, J_{AB} = 16.0 Hz, J_{BX} = 8.6 Hz, 1 H), 2.10–1.93 (m, 2 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.75 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 153.7, 141.1, 139.2, 129.1, 128.7, 125.9, 114.7, 69.9, 57.6, 41.7, 39.9, 34.1, 17.0, 15.9. HRMS: *m/z* calcd for $C_{17}H_{21}O_3N$ $[M]^+$: 287.1521; found: 287.1521.

Synthesis of 7

A 30% aq solution of H_2O_2 was added slowly to a solution of oxazolidinone **4** (0.36 g, 1.3 mmol) in THF–H_2O (4:1, 6 mL) at 0 °C. A solution containing LiOH·H_2O (73 mg, 1.7 mmol) in H_2O (4 mL) was added slowly to the reaction mixture. The reaction was left to stir at 0 °C for 1 h, at which point it was quenched by the addition of a solution containing Na_2SO_3 (0.64 g, 5.1 mmol) in H_2O (4 mL). The THF was removed in vacuo and the basic solution extracted with CH_2Cl_2 (3 × 10 mL) to remove the chiral auxiliary. The remaining aqueous layer was cooled to 0 °C, acidified with 6 N HCl to pH ca. 1 and extracted with EtOAc (5 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 0.17 g (94%) of **7** as a clear oil; R_f = 0.5 (hexanes–EtOAc = 4:1). FTIR (thin film): 3500–2500, 2966, 1716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.76–5.62 (m, 1 H), 5.04–4.96 (m, 2 H), 2.44–2.34 (m, 1 H), 2.24–1.96 (m, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.928 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 141.0, 115.0, 42.2, 39.1, 35.0, 17.6, 16.2. HRMS: *m/z* calcd for $C_8H_{15}O_2$ $[M + H]^+$: 143.1072; found: 143.1073.

Synthesis of 9

Ozone gas was bubbled through a solution of alkene **7** (194 mg, 1.36 mmol) in dry CH_2Cl_2 (14 mL) at –78 °C until a light blue color persisted (ca. 5 min). Oxygen gas was then bubbled through the solu-

tion until the blue color dissipated, at which point Ph_3P (393 mg, 1.50 mmol) was added in one portion. The reaction was warmed to r.t. and left to stir overnight at which point it was concentrated and filtered through a plug of silica gel (hexanes–EtOAc = 2:1) to yield **8**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.86 (d, *J* = 1.7 Hz, 1 H), 2.52–2.38 (m, 3 H), 2.30–2.20 (m, 1 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.08 (d, *J* = 5.8 Hz, 3 H). $NaBH_4$ (102 mg, 2.72 mmol) was added to a solution of the resulting aldehyde **8** (1.36 mmol) in aq THF at r.t. After stirring for 12 h, the reaction was acidified to pH 1 by the addition of concd H_2SO_4. The mixture was diluted with H_2O (30 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with sat. aq $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes–EtOAc = 4:1) to afford 130 mg (75%) of **9** as a clear oil; R_f = 0.3 (hexanes–EtOAc = 4:1). FTIR (thin film): 2964, 1732 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 (dd, *J* = 11.3, 4.4 Hz, 1 H), 4.12 (dd, *J* = 9.9, 6.9 Hz, 1 H), 2.61 (dd, *J* = 18.1, 6.0 Hz, 1 H), 2.30 (dd, *J* = 18.1, 7.7 Hz, 1 H), 2.20–2.05 (m, 2 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 73.4, 36.4, 31.2, 29.9, 15.8, 11.5. HRMS: *m/z* calcd for $C_7H_{13}O_2$ [M + H]$^+$: 129.0916; found: 129.0910.

Synthesis of (–)-Lasiol (1)

DIBAL-H (1.0 M in toluene, 1.8 mL, 1.8 mmol) was added to a solution of lactone **9** (0.16 g, 1.3 mmol) in dry CH_2Cl_2 (13 mL) at –78 °C. After stirring at –78 °C, the reaction was quenched with EtOAc and allowed to warm to r.t. Sat. aq Rochelle salt (15 mL) was added and the reaction mixture allowed to stir vigorously for 14 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes–EtOAc = 4:1) to afford 0.14 g (87%) of **10** as a mixture of diastereomers.

n-BuLi (2.0 M in hexanes, 1.1 mL, 2.2 mmol) was added dropwise to isopropyltriphenylphosphonium iodide (0.94 g, 2.2 mmol) dissolved in dry THF (5 mL) at 0 °C. Following addition of *n*-BuLi, the deep red reaction mixture was stirred at 0 °C for 5 min before being cooled to –78 °C. To this mixture was added a solution of lactol **10** (120 mg, 0.91 mmol) in dry THF (5 mL) over the course of 5 min. After stirring at –78 °C for 30 min, the reaction mixture was transferred to an ice–water bath and allowed to warm to 0 °C over the course of 1 h. The reaction was quenched by the addition of sat. aq NH_4Cl (5 mL) and diluted with EtOAc (15 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes → hexanes–EtOAc = 6:1) to afford 66 mg (47%) of (–)-lasiol (**1**) as a clear oil; R_f = 0.5 (hexanes–EtOAc = 4:1); $[\alpha]_D^{24}$ –8.0 (*c* 1.9, *n*-hexane). FTIR (thin film): 3333, 2964 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07–5.14 (m, 1 H), 3.64 (A of ABX, J_{AB} = 10.4 Hz, J_{AX} = 5.5 Hz, 1 H), 3.46 (B of ABX, J_{AB} = 10.4 Hz, J_{BX} = 7.03 Hz, 1 H), 2.09–1.99 (m, 1 H), 1.85–1.74 (m, 1 H), 1.69 (s, 3 H), 1.68–1.47 (m, 2 H), 1.59 (s, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.1, 123.5, 66.2, 40.2, 35.5, 31.4, 25.8, 17.8, 17.0, 13.8. HRMS: *m/z* calcd for $C_{10}H_{20}O$ [M]$^+$: 156.1509; found: 156.1502.

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References and Notes

(1) Lloyd, H. A.; Jones, T. H.; Hefetz, A.; Tengö, J. *Tetrahedron Lett.* **1990**, *31*, 5559.
(2) Kasai, T.; Watanabe, H.; Mori, K. *Bioorg. Med. Chem.* **1993**, *1*, 67.
(3) Kuwahara, S.; Shibata, Y.; Hiramatsu, A. *Liebigs Ann. Chem.* **1992**, 993.
(4) Donaldson, W. A.; Jin, M.-J. *Tetrahedron* **1993**, *49*, 8787.
(5) Vasil'ev, A. A.; Vielhauer, O.; Engman, L.; Pietzsch, M.; Serebryakov, E. P. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 481.
(6) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610.
(7) Schneider, C. *Eur. J. Org. Chem.* **1998**, 1661.
(8) van Zijl, A. W.; Szymanski, W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 6994.
(9) Asano, S.; Tamai, T.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2003**, 2252.
(10) (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3.
(11) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(12) For representative examples, see: (a) Williams, D. R.; Nold, A.; Mullins, R. J. *J. Org. Chem.* **2004**, *69*, 5374. (b) Williams, D. R.; Li, J. J. *Tetrahedron Lett.* **1994**, *35*, 5113. (c) Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217. (d) White, J. D.; Lee, C.-S.; Xu, Q. *Chem. Commun.* **2003**, 2012.
(13) For representative examples, see: (a) Nicolás, E.; Russell, K.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766. (b) Li, G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, 2561. (c) Liao, S.; Han, Y.; Qui, W.; Bruck, M.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 7917.
(14) (a) Wu, M.-J.; Wu, C.-C.; Lee, P. C. *Tetrahedron Lett.* **1992**, *33*, 2547. (b) Wu, M.-J.; Yeh, J.-Y. *Tetrahedron* **1994**, *50*, 1073.
(15) Faveau, C.; Mondon, M.; Gesson, J.-P.; Mahnke, T.; Gebhardt, S.; Koert, U. *Tetrahedron Lett.* **2006**, *47*, 8305.
(16) Williams, D. R.; Mullins, R. J.; Miller, N. A. *Chem. Commun.* **2003**, 2220.
(17) The facial selectivity observed in the organocopper reactions has been rationalized by addition to the face opposite the bulky phenyl group in a bidentate Lewis acid complex first proposed by D. A. Evans[11] and subsequently characterized: Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.
(18) A similar reversal in facial selectivity for conjugate addition of *O*-benzylhydroxylamine has been reported: Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615.
(19) The relative and absolute stereochemistry of the major product **4** was proven via X-ray crystallography, see ref. 16.
(20) Similar endgame has been utilized in previous lasiol syntheses, see ref. 1 and 2.