Enantioselective Total Synthesis of (−)-Hunterine A Enabled by a Desymmetrization/ Rearrangement Strategy

Elliot F. Hicks, Kengo Inoue, and Brian M. Stoltz*

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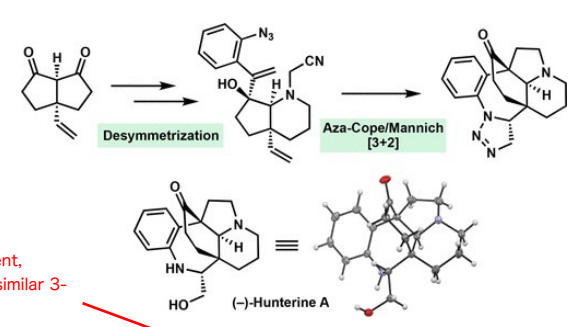

monoterpene indole alkaloids (MIAs)

C7 quaternary center via an aza-Cope/Mannich rearrangement, developed by Overman and co-workers for the synthesis of similar 3-acyl pyrrolidine motifs,

Scheme 2. (A) Synthesis of Keto-Alcohol 10; (B) Advancement of 10 to Ketone 5 Using a Beckmann Rearrangement; (C) Completion of (−)-Hunterine A

optimized :the Grignard is added to all other reagents at –40 °C

umpolung ylide addition

the iminium precursor

deprotonation

vinyl dianion nucleophile optimization

Table 1. Desymmetrization of Diketone 6

Entry	Catalyst[a]	Reductant	Solv./Temp./Time	Conversion[c]	10:11	ee
1	Baker's yeast, yeast extract	–	H_2O:DMSO (70:1) 25 °C, 48 h	30%	1 : 0	–95%
2	(S)-n-Bu-CBS	catecholborane	toluene –78 °C, 3 h	40%	–	–
3	RuCl(p-cymene) [(R,R)-Ts-DPEN][b]	i-PrOH	i-PrOH, 28 °C 24 h	<5%	n.d.	n.d.
4	RuCl(mesitylene) [(R,R)-Ts-DPEN][b]	i-PrOH	i-PrOH, 28 °C 24 h	20%	1 : 0	15%
5	RuCl(mesitylene) [(R,R)-Ts-DPEN]	HCOOH:Et_3N (5:2) (2 equiv)	CH_2Cl_2 28 °C, 14 h	88%	1 : 1.2	79%
6	RuCl(mesitylene) [(R,R)-Ts-DPEN]	HCOOH:Et_3N (5:2) (2 equiv)	THF 28 °C, 14 h	99%	1 : 1	82%
7	RuCl(mesitylene) [(R,R)-Ts-DPEN]	HCOOH:Et_3N (5:2) (2 equiv)	1,4-dioxane 28 °C, 14 h	99%	1 : 0.6	91%
8	RuCl(mesitylene) [(R,R)-Ts-DPEN]	HCOOH:Et_3N (5:2) (1.5 equiv)	1,4-dioxane 28 °C, 14 h	95%	1 : 0.3	85%
9	RuCl(mesitylene) [(R,R)-Ts-DPEN]	HCOOH:Et_3N (5:2) (1 equiv)	1,4-dioxane 28 °C, 14 h	90%	1 : 0.12	81%

[a]Reactions were conducted with 1 mol % [Ru] catalyst. [b]Five mol % KOH added. [c]Conversion determined by the ^{1}H NMR ratio of the remaining diketone **6** relative to the CH_2Br_2 internal standard.

the desymmetrization of other symmetrical diketone substrates is currently underway.

Scheme 3. Divergent Access to (−)-Aspidospermidine via Aniline 18

Scheme 4. Reactivity Differences between Triazoline 20 and C19-epi-20 and Nitrogen Pyramidality

Noyori's transfer hydrogenation conditions

triazoline 20 — 345°, 45% pyramidal

C19-epi-20 — 357°, 9% pyramidal

propensity to retain a planar geometry