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**FROM AMINO ACIDS TO POLYCYCLIC HETEROCYCLES -  
SYNTHESIS OF ENANTIOPURE, FUNCTIONALLY DIVERSE  
ISOPAVINES AND DIHYDROMETHANODIBENZOAZOCINES‡**

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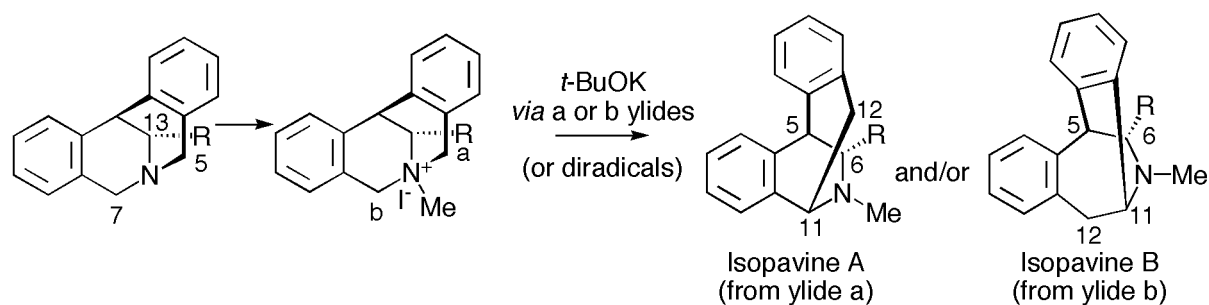
**Abstract** – The intramolecular double Friedel-Crafts condensation of *N,N*-dibenzyl-*O*-benzyl-*L*-threoninal affords a rearranged tetracyclic compound involving a methyl migration. *N*-Demethylation of tetracyclic isopavines leads to topologically unique secondary amines with potential utility in catalytic reactions as a chiral basic ligand.

## INTRODUCTION

The isopavine alkaloids,<sup>1</sup> isolated from the Papaveraceae family are endowed with important pharmacological activities related to a number of severe disease conditions such as Alzheimer's, Parkinson's and Down's syndrome.<sup>2</sup> The potential CNS effects of diarylazocines have been known for some time.<sup>3</sup> Several syntheses of these classes of nitrogen heterocycles utilizing a variety of approaches have been reported over the years.<sup>1,4</sup> However, methods that lead to enantiopure products have only recently been addressed.<sup>5</sup> In previous publications, we reported new syntheses of functionalized isopavines<sup>6</sup> and dihydromethanodibenzoazocines<sup>7</sup> with versatile functional groups that could be further manipulated and diversified. For example, isopavines with substituents at C-6 could be easily obtained in one step via a [1,2]-Stevens rearrangement of a 13-substituted *N*-methyl-dihydromethano-dibenzoazocinium ion (Scheme 1).

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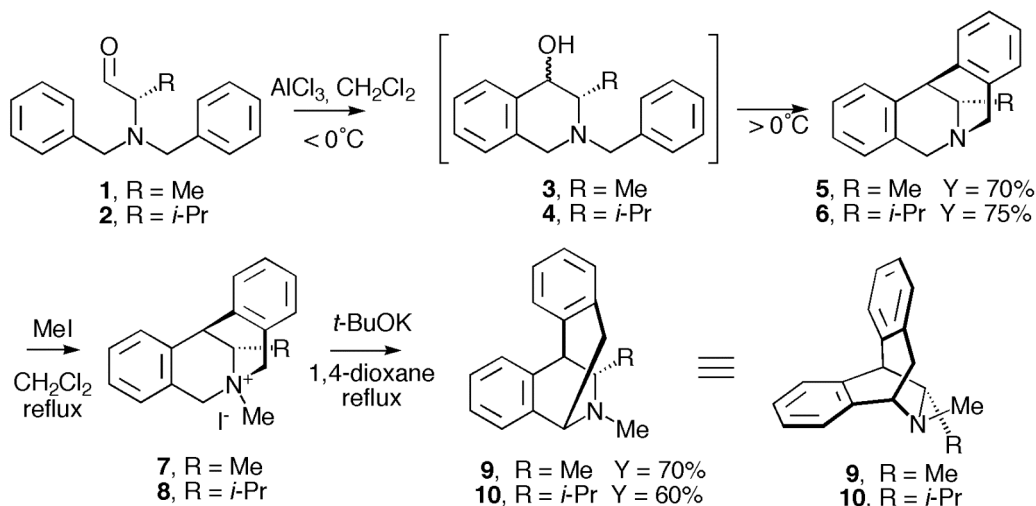
‡ This paper is dedicated to Professor Barry M. Trost at the occasion of his 65th birthday anniversary, wishing him the best in life and in chemistry.



**Scheme 1** [1,2]-Stevens rearrangement leading to isopavine A when R = alkyl, benzyl,  $(\text{CH}_2)_n\text{OPiv}$ , *N*-*t*-Boc-3-indolylmethyl formed *via* ylide at position "a"

Such a rearrangement can lead to two isomeric isapavines A and B, depending on which ylide (or its diradical equivalent) is formed.<sup>6</sup> Only isopavines of type A were formed in the case of *N*-methyl substituted "azocinium ions" as shown in Scheme 1. In practice, *N,N*-dibenzylamino acids, easily obtained from natural or unnatural  $\alpha$ -amino acids were transformed into the corresponding aldehydes<sup>8</sup> (Scheme 2). Exposure to  $\text{AlCl}_3$  under mild conditions led first to the tetrahydroisoquinolines (**3**) and (**4**), which could be isolated, or allowed to undergo a second Friedel-Crafts type cyclization by nucleophilic attack of the second *N*-benzyl group onto an incipient benzylic carbocation. The corresponding desymmetrized dihydromethanodibenzoazocines (**5**) and (**6**) with pendant alkyl groups (or other usable functionality) at C-13 were isolated as crystalline solids in high yields.<sup>6,7</sup>

Transformation to the *N*-methyl "azocinium" salts (**7**) and (**8**), followed by refluxing in 1,4-dioxane containing *t*-BuOK gave the corresponding 6-methyl- and 6-isopropylisopavines (**9**) and (**10**) in good overall yields<sup>6,7</sup> and the same procedure was applied to other functionalized analogues. Extensive studies on the Stevens rearrangement<sup>9,10</sup> have postulated the intermediacy of *N*-ylides which are converted to iminium ions (or their diradical equivalents).

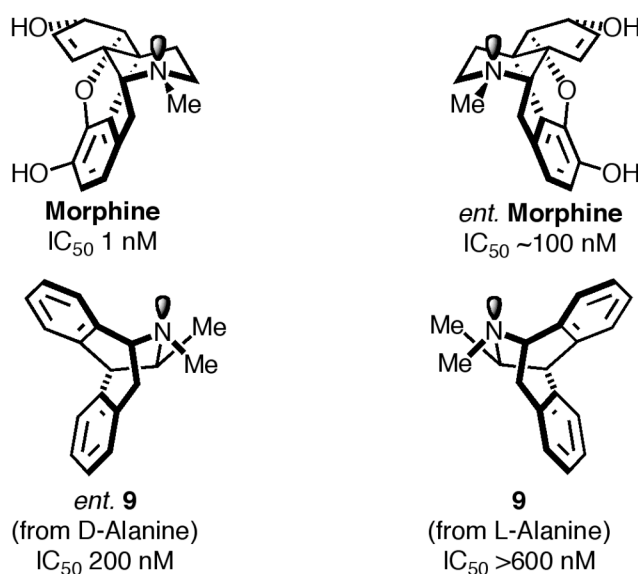


**Scheme 2** Intramolecular Friedel-Crafts reaction and [1,2]-Stevens rearrangement to type A isopavines

When viewed in their three dimensional perspective structures, the aryl rings in "azocines" and isopavines adopt a mutually orthogonal orientation with respect to the plane of the commonly shared tetrahydroisoquinoline as evidenced by X-Ray ORTEP diagrams.<sup>6,7</sup>

The power of visual imagery manifested itself in a Dalièsque fashion, when it was realized that a very close spatial relationship existed between a rigid tricyclic isopavine nucleus such as **9** and morphine (Figure 1).<sup>11</sup> Further scrutiny, especially with regard to the all-important orientation of the lone pair of electrons on the tertiary amine<sup>12</sup> led us to consider a D-amino acid such as D-alanine as the source of chirality, leading to *ent.* (**9**). Indeed, when comparing the  $\mu$ -receptor binding affinities, it was found that *ent.* (**9**) (which shows an excellent skeletal overlap with morphine) was at least three times more active than **9**, which corresponds to the enantiomer of morphine (Figure 1). Further fine-tuning of substituents, especially on the aromatic rings led to analogues with low nM  $\mu$ -receptor binding affinity approaching that of morphine itself.<sup>11</sup>

We report herein some observations regarding the synthesis of dihydromethanodibenzoazocines from L-threonine, as well as the *N*-dealkylation of isopavines (**9**) and (**10**) leading to topologically interesting chiral secondary amines.

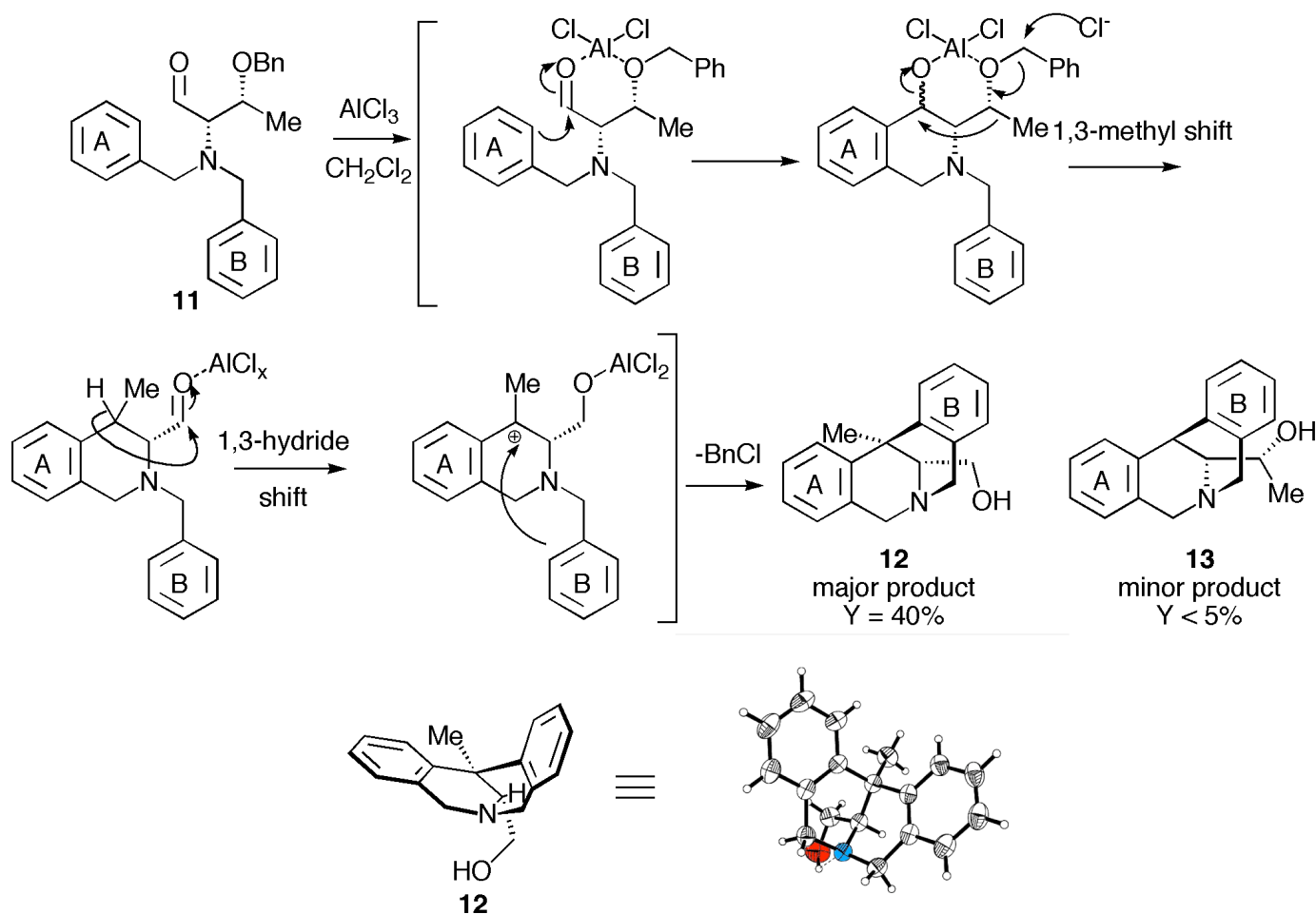


**Figure 1** Topological and structural analogy between enantiomeric isopavines and corresponding morphines

## RESULTS AND DISCUSSION

Previous studies from our group had shown that a variety of  $\alpha$ -substituted amino aldehydes including L-serine were cyclized under Friedel-Crafts conditions as discussed above.<sup>6,7</sup> In an effort to extend the

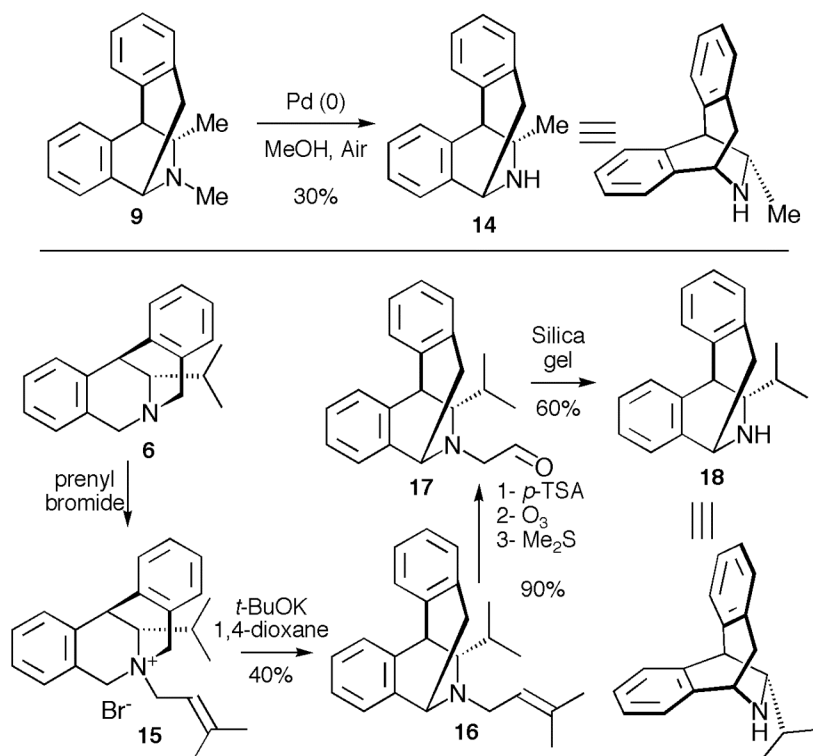
reaction to *O*-benzyl-L-threoninal (**11**),<sup>8</sup> we encountered an unexpected reaction course. In fact, the major isolable product was found to be the rearranged "azocine" (**12**) (Scheme 3). Although more than one pathway can be envisaged,<sup>13a</sup> a plausible mechanism for this reaction could involve an intramolecular Friedel-Crafts cyclization by the *N*-benzyl group designated as A (Scheme 3) of a coordinated aldehyde intermediate. The resulting tetrahydroisoquinoline aluminate complex now loses the benzyl group as the chloride followed by sequential [1,3]-methyl and [1,3]-hydride shifts leading to a bicyclic benzylic carbocation. A second intramolecular attack by the *N*-benzyl group designated as B in Scheme 3 generates the observed 5-methyl branched "azocine" (**12**). The structure and relative stereochemistry was ascertained by X-Ray crystal analysis (Scheme 3). Only a negligible quantity of the expected C-13 branched hydroxyethyl "azocine" (**13**) was observed. An alternative pathway which would involve ring A phenyl migration on a secondary carbocation generated from loss of the *O*-benzyl ether would in fact lead to the enantiomer of (**12**).<sup>13b</sup> <sup>1</sup>H- and <sup>13</sup>C-NMR spectral analysis of the (*R*)-Mosher ester prepared from (**12**) indicated that only a single diastereomer was present. However, the absolute configuration at C-13 of the rearrangement product (**12**) is not known at this time.



Scheme 3

The orthogonal orientation of the aryl groups with regard to the plane of the commonly shared tetrahydroisoquinoline in the azocines and isopavines as depicted in Figure 1 suggests interesting possibilities for ligand design and applications to catalysis.<sup>14</sup> To this end, we proceeded to explore methods to de-*N*-alkylate isopavines (**9**) and (**10**) with the intention of preparing the corresponding topologically novel and spatially constrained secondary amines.<sup>15</sup>

We first explored a method based on an oxidative de-*N*-methylation in the presence of Pd (0) and air.<sup>16</sup> The proposed mechanism involves the formation of an oxido-Pd specie, which is transformed to an *N*-hydroxymethylcarbinolamine before losing formaldehyde and generating the secondary amine. Under the reported conditions,<sup>16</sup> isopavine (**9**) led to a poor yield of the the expected product (**14**) (Scheme 4). Extension to other alkyl isopavines was not succesful and this led us to explore other methods for the *N*-dealkylation of isopavines. Thus, **6** was treated with prenyl bromide to give the corresponding "azocinium ion" (**15**). Upon treatment with *t*-BuOK in refluxing 1,4-dioxane, a smooth [1,2]-Stevens rearrangement took place to give **16**. Protonation with *p*-TsOH, and treatment the resulting salt, with ozone at -78 °C followed by conventional workup with dimethylsulfide, gave aldehyde (**17**). Stirring of (**17**) in a suspension of chromatography grade silica gel and EtOAc containing *ca.* 5% of water gave the amine (**18**) in 25% overall yield from **6** (Scheme 4). When viewed in a different perspective, isopavines (**14**) and (**18**) present interesting topologies with orthogonally oriented heteroaromatic residues as shown in Scheme 4.



Scheme 4

## EXPERIMENTAL

**GENERAL EXPERIMENTAL DETAILS:** Solvents were distilled under positive pressure of dry nitrogen before use and dried by standard methods: THF and ether, from K/benzophenone; CH<sub>2</sub>Cl<sub>2</sub> and toluene from CaCl<sub>2</sub>. All commercially available reagents were used without further purification. All reactions were performed under nitrogen atmosphere. NMR (<sup>1</sup>H, <sup>13</sup>C) spectra were recorded on ARX-400 or AV-400 spectrometers in CDCl<sub>3</sub> or CD<sub>3</sub>OD with tetramethylsilane as the internal standard. In some cases, carbon resonances were coincident. Low- and high-resolution MS spectra were recorded on AEI-MS 902, spectrometers using fast atom bombardement (FAB) or electrospray techniques. Optical rotations were recorded on a PE241 polarimeter in a 1 dm cell at ambient temperature. Analytical TLC was performed on Merck 60F<sub>254</sub> precoated silica gel plates. Visualization was performed by UV or by development using KMnO<sub>4</sub> or FeCl<sub>3</sub> solutions. Flash column chromatography was performed using silica gel (40-60 μm) at increased pressure. Melting points recorded were uncorrected.

### (13R)-(12-Methyl-7,12-dihydro-5H-6,12-methanodibenzo[*c,f*]azocin-13-yl)methanol (12)

In 15 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to -78 °C were added successively under argon atmosphere, oxalyl chloride (440 μL, 5 mmol), dry DMSO (700 μL, 10 mmol), slowly so as not to create pressure in the flask. This mixture was stirred 10 minutes at -78 °C prior to adding alcohol (**11**)<sup>8b</sup> (361 mg, 1 mmol) dissolved in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>. The colorless solution was stirred at -78 °C for an hour, then triethylamine (2 mL, *ca.* 15 mmol) was added. Temperature was allowed to rise to 0 °C, then 5 to 10 mL of water were added to the milky mixture. Extraction with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL) and washing of the organic layers with 30 mL of 1% HCl, water, NaHCO<sub>3</sub> and brine followed by drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration gave a colorless syrup. A suspension of aluminium chloride (667 mg, 5 mmol) in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> was prepared and cooled to 0 °C. The aldehyde was dissolved in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>, and the solution was added to the suspension of aluminium chloride. The mixture which turned from yellow to deep carmine red was stirred for 1 h while warming up to rt then poured into a saturated solution of NaHCO<sub>3</sub> (*ca.* 20 ml) and ice (*ca.* 20 ml). Sodium potassium tartrate (*ca.* 5 g) was added and the mixture was allowed to stir overnight or until the water phase became almost clear. Five successive extractions with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and usual processing of the organic extracts afforded 425 mg of a dark red oil that was purified by chromatography using silica gel (100% EtOAc then 7% MeOH/EtOAc). Product (**13**) (*ca.* 10 mg, < 5% yield) was found only as an impurity and wasn't recovered pure by chromatography. The purified product (**12**) was recovered as a white crystalline solid, (105 mg, 40%) which was recrystallized from hot EtOAc to provide an analytical sample for X-Ray diffraction; R<sub>f</sub> = 0.05 (100% EtOAc); [α]<sub>D</sub><sup>20</sup> -14.3° (*c* 1, CHCl<sub>3</sub>); mp 88-92 °C (from hot EtOAc). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45-7.41 (m, 2H); 7.15-6.92 (m, 2H); 4.61 (d, J = 17.4 Hz,

1H); 4.53 (d,  $J = 18.6$  Hz, 1H); 4.08 (d,  $J = 17.4$  Hz, 1H); 3.85 (d,  $J = 18.6$  Hz, 1H); 3.80 (dd,  $J = 3.5$  and  $9.3$  Hz, 1H); 3.41-3.33 (m, 2H); 1.74 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.5; 142.0; 134.4; 134.3; 127.6; 127.3; 127.1; 126.9; 126.0; 125.9; 125.3; 124.3; 64.3; 60.8; 59.1; 52.5; 35.5; 20.1. HRMS for ( $M + 1$ )  $\text{C}_{18}\text{H}_{20}\text{NO}$ : calcd: 266.1466, found 266.1453.

**(5R,6S,12S)-6-methylisopavine (14)**: Five 30 mL test tubes containing 0.5 mL of methanol and 50 mg of palladium-on-charcoal (10%) were prepared by a very careful addition of the catalyst under regular air atmosphere. Isopavine (**9**) (250 mg, 1 mmol) dissolved in 2.5 mL of methanol was equally divided in the 5 test tubes containing the catalyst (0.5 mL in each), and the suspensions were stirred vigorously in an open air atmosphere for 3-4 days at rt. The mixtures were then filtered over Celite, the filtrates were combined then treated with 5 mL of 6 *N* HCl for 12 h. The solution was neutralized with sodium carbonate until blue to litmus ( $\text{pH} \gg 9$ ), then extracted with 20% MeOH/ $\text{CH}_2\text{Cl}_2$  (5 x 100 mL), and the combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , then concentrated under vacuum to give 120 mg of a brown oil which was purified by chromatography using 10% MeOH/ $\text{CH}_2\text{Cl}_2$  as eluant. Product (**14**) (70 mg, 30%) was obtained as a yellow oil;  $R_f = 0.05$  (100% EtOAc);  $[\alpha]_D^{20} -110^\circ$  ( $c$  1,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.15-6.95 (m, 8H); 4.28 (t,  $J = 3.7$  Hz, 1H); 3.93 (q,  $J = 6.5$  Hz, 1H); 3.60 (s, 1H); 3.52 (dd,  $J = 3.7$  and  $17.7$  Hz, 1H); 3.22 (dd,  $J = 3.7$  and  $17.7$  Hz, 1H); 1.10 (d,  $J = 6.5$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  143.1; 139.7; 139.3; 138.8; 131.1; 127.6; 127.0; 126.9; 126.6; 126.4; 125.7; 124.4; 55.6; 54.8; 52.8; 39.6; 23.7. HRMS for ( $M + 1$ )  $\text{C}_{17}\text{H}_{18}\text{N}$ : calcd: 236.1361, found: 236.1360.

**(5R,6S,12S)-N-(2'-Methylbut-2'-en-4'-yl)-6-isopropylisopavine (16)**: Azocine **5** (263 mg, 1 mmol) was dissolved in a minimum volume of acetone (*ca.* 0.5 mL). Prenyl bromide was added (150  $\mu\text{L}$ , 1.5 mmol) and the solution was heated under reflux until a white precipitate (15 min) appeared. Ether was added to the white suspension (5 to 10 mL) to help disperse the solid. The supernatant liquid was decanted and the solids washed with fresh ether (3 x 10 mL), dried under vacuum and suspended in 7 mL of THF. This mixture was cooled to  $-15^\circ\text{C}$  prior to adding a solution of potassium *t*-butoxide in THF (3 mL, 3 mmol). After stirring for 1 h at  $-15^\circ\text{C}$ , water (10 mL) was added and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 mL). The combined organic extracts were washed with brine and dried on  $\text{Na}_2\text{SO}_4$ . Concentration under vacuum afforded a brown oil (250 mg) that was purified by silica gel column chromatography (EtOAc/Hexanes) to give **16** as a colorless oil (130 mg, 40%);  $R_f = 0.4$  (5% EtOAc/Hexanes);  $[\alpha]_D^{20} -99.4^\circ$  ( $c$  1,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23-7.00 (m, 8H); 5.38-5.34 (m, 1H); 4.23 (t,  $J = 3.3$  Hz, 1H); 3.83 (s, 1H); 3.66 (dd,  $J = 3.3$  and  $18.1$  Hz, 1H); 3.52 (dd,  $J = 8.8$  and  $14.3$  Hz, 1H); 3.28 (dd,  $J = 1.6$  and  $14.3$  Hz, 1H); 2.86 (d,  $J = 6.3$  Hz, 1H); 2.82 (dd,  $J = 3.3$  and  $18.1$  Hz, 1H); 1.80 (s, 3H); 1.74 (s,

3H); 1.68-1.56 (m, 1H); 1.00 (d,  $J = 6.9$  Hz, 3H); 0.71 (d,  $J = 6.8$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  143.7; 140.7; 140.6; 135.7; 133.7; 131.1; 127.3; 126.9; 126.0; 126.0; 125.7; 125.7; 124.5; 123.3; 72.3; 56.5; 50.9; 48.0; 33.3; 32.5; 25.9; 20.2; 18.2; 18.1. HRMS for (M + 1)  $\text{C}_{24}\text{H}_{30}\text{N}$ : calcd: 332.2379, found: 332.2368.

**(5R,6S,12S)-6-Isopropylisopavine (18)**: *N*-Prenylisopavine (**16**) (331 mg, 1 mmol) and *p*-toluenesulfonic acid (950 mg, 5 mmol) were dissolved in 10 mL of a 1:1 mixture of MeOH and  $\text{CH}_2\text{Cl}_2$ . After cooling to  $-78$  °C, ozone was bubbled through the solution for 1 h, and excess ozone was flushed out by bubbling argon for 15 min, prior to adding dimethyl sulfide (1 mL, *ca.* 20 mmol). The solution was allowed to warm to room temperature, carefully neutralized with a saturated solution of  $\text{NaHCO}_3$  (*ca.* 10 mL), then extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 50 mL). The combined organic layers were washed with brine and dried with sodium sulfate. The concentrated residue consisting of the aldehyde (**17**) (pale yellow oil, 380 mg) was diluted with 20 mL of EtOAc and silica gel was added to the mixture (*ca.* 10 mL) as well as 1 mL of water. The suspension was allowed to stir for 6 h at room temperature and the crude product (**18**) was recovered by eluting the product from the silica with pure EtOAc; ( $R_f = 0.05$ , 50% EtOAc/Hexanes) to give a white crystalline solid (155 mg, 60% overall yield) that was recrystallized from EtOAc/hexanes; mp  $74$ - $78$  °C;  $[\alpha]_D^{20} -78.3^\circ$  (*c* 1,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25-7.05 (m, 8H); 4.30 (t,  $J = 3.3$  Hz, 1H); 3.85 (s, 1H); 3.50-3.42 (m, 2H); 3.23 (dd,  $J = 3.3$  and  $17.9$  Hz, 1H); 1.55-1.45 (m, 1H); 0.90-0.85 (m, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.2; 140.3; 135.9; 131.1; 127.2; 126.3; 126.2; 126.2; 125.7; 125.7; 124.5; 124.2; 66.0; 54.8; 48.5; 39.6; 33.6; 19.2; 18.9. HRMS for (M + 1)  $\text{C}_{19}\text{H}_{22}\text{N}$ : calcd: 264.1523, found: 264.1531.

## ACKNOWLEDGEMENTS

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  13. a) The same sign of rotation observed for **12** and its des-C-5-methyl analogue (ref. 7), leads us to assign a (13*R*) stereochemistry as shown in Scheme 3. b) A reviewer has also suggested such an alternative pathway.
  14. For authoritative reviews, see E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, *Comprehensive Asymmetric Catalysis, Vol. I-III*, Springer, New York, 1999.
  15. For secondary amines in organocatalysis, see P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2001, **40**, 3726.
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