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AN ASYMMETRIC SYNTHESIS (-)-EPIBATIDINE

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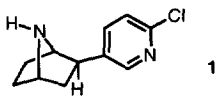
Summary: A Pd catalyzed desymmetrization of cis-3,6-dibenzoyloxy-2-cyclohexene and a Pd catalyzed cross-coupling constitute key reactions in a synthesis of the non-opioid analgesic (-)-epibatidine.

In 1992, NIH investigators isolated an unusual new alkaloid from the skin extracts of the Equadoran frog *Epipedobates tricolor*, (-)-epibatidine (**1**).[1] Biological investigations revealed a number of activities, a



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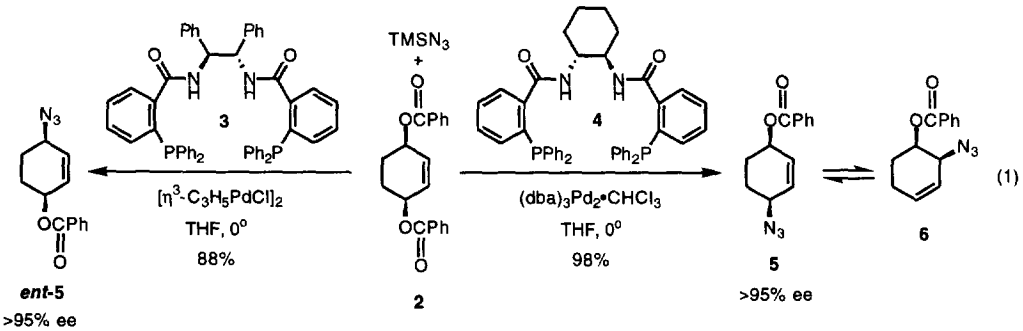
most significant one emanating from its being 200-500 times more analgesic than morphine but devoid of opiate activity.[2] Its low natural abundance (<1 mg from 750 frogs) combined with its biological activity stimulated numerous synthetic efforts.[3] Remarkably, in spite of the intense activity, there exists no asymmetric synthesis of this target. Its availability in enantiomeric pure forms have only occurred through resolution at some point in the synthesis of the final product.[4] Several strategies directed towards an asymmetric synthesis have been recorded but have not yet culminated in an enantioselective synthesis.[5] We record an asymmetric synthesis of (-)-epibatidine that can provide entry into either enantiomer which proceeds through the Boc derivative of enantiomerically pure 4-aminocyclohex-2-enone (**9**), a potentially versatile intermediate.

As previously noted,[6] subjecting dibenzoate **2** and trimethylsilylazide (1:1) to a catalyst derived from π-allylpalladium chloride dimer and **3**[7] gave ent-**5** in 88% yield and >95% ee with a small amount of the doubly



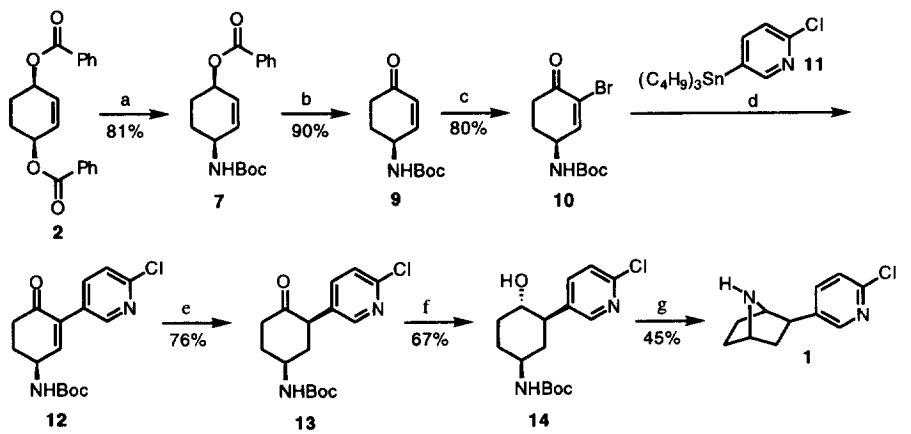
substituted bis-azide (monoazide:bis-azide, >17:1). Using the cyclohexyl ligand **4**[7] in the same reaction reveals a different issue. Double azidation did not occur. However, a small amount of the allylically rearranged azide **6**

accompanied the desired product **5** (**5**:**6**, 92:8) in a reaction that proceeded nearly quantitatively and in excellent ee (>95%). The amount of azide **6** is minimized by 1) reducing the amount of catalyst and 2) monitoring the reaction time so it is stopped upon completion. These observations reinforce the earlier suggestion[6] that the rearranged azide may derive from a Pd(0) catalyzed event rather than a simple thermal process, especially since the reactions are performed at 0°.

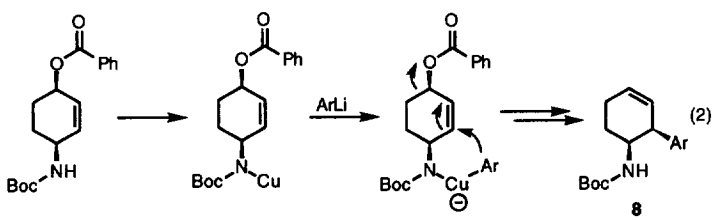
The scheme outlines the synthesis of (-)-epibatidine starting from dibenzoate **2**. Synthetically, for the desymmetrization event (**2**→**7**), it was most convenient to simply add pentane to the Pd(0) catalyzed asymmetric alkylation, filter the resultant heterogeneous mixture through a plug a silica gel, dissolve the crude azide in a 2:1 THF-water mixture at room temperature to which is added 1.2 equiv. of trimethylphosphine followed by adding di-*tert*-butyldicarbonate and triethylamine. In this way, an 81% yield of the Boc-amide **7**,[8] mp 78-79°C, $[\alpha]_D^{23}$ +86.6 (c = 1.26, CH_2Cl_2), is isolated.

Initial attempts for introduction of the pyridyl unit explored the direct arylation of **7**. The establishment of the *cis* relationship of the aryl group and the amine was envisioned to derive from a neighboring group participation as outlined in eq. 2 wherein **8** would constitute the epibatidine precursor.[9] Initial attempts did not

Scheme. A Synthesis of (-)-Epibatidine



(a) (i) 0.25 mol% $[\eta^3\text{-}C_3H_5PdCl]_2$, 0.75 mol% **4**, 1.2 equiv. $TMSN_3$, THF, 0°; (ii) $(CH_3)_3P$, 2:1 THF-H_2O, 1.2 equiv. $(CH_3)_3P$, r.t. then add $(t\text{-}C_4H_9OCO)_2O$, $(C_2H_5)_3N$. (b) K_2CO_3, CH_3OH, r.t. then Dess-Martin periodinane, CH_2Cl_2, r.t. (c) Br_2, $(C_2H_5)_3N$, CH_2Cl_2, 0°. (d) 2.5 mol% $(dba)_3Pd{\bullet}CHCl_3$, 15 mol% Ph_3As, THF, 55°. (e) K-selectride, THF, -78° to 0° then cat. DBU, THF, (f) $NaBH_4$, CH_3OH, 0°. (g) CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2, 0°; CF_3CO_2H, H_2O, r.t.; CH_3CN, reflux.



look promising. Furthermore, the instability of the lithium and copper species derived from 5-bromo-2-chloropyridine[10] led us to abandon further efforts in this direction. An alternative envisions conjugate addition to an enone **9** which might also proceed *cis* to the amide either via axial attack on a half-chair cyclohexene with the Boc-amide substituent equatorial or by complexation of the organometallic to the amide group and internal delivery of the aryl unit. The requisite cyclohexenone **9**, mp 117-8°, $[\alpha]_D^{23}$ -123.6 (c = 1.14, CH_2Cl_2), is derived from base hydrolysis of the benzoate and oxidation.[11] Again, the instability of the organometallic derived from the pyridine subunit thwarted these efforts.

A satisfactory solution for introduction of the aryl group utilized the stable organostannane **11**. The latter arises from 5-bromo-2-chloropyridine by two sequential metal-halogen exchanges, first with n-butyllithium then with tri-n-butyltin chloride, in 93% yield. Pd(0) catalyzed cross-coupling with the vinyl bromide **10**, mp 141-2°, $[\alpha]_D^{23}$ -111.7 (c = 1.24, CH_2Cl_2), proceeded in excellent yield with triphenylarsine as ligand[12] to give enone **12**, mp 136-7°, $[\alpha]_D^{23}$ -82.3 (c = 0.29, CH_2Cl_2).

Chemoselective reduction of the double bond with K-selectride[13] generates an 88% yield of a 4:1 *cis*:*trans* mixture from which the pure *cis* isomer **13**, mp 198-9°, $[\alpha]_D^{23}$ -16.4 (c = 1.03, CH_2Cl_2), can be isolated by recrystallization. Equilibration of the mother liquors with DBU (THF, rt) and crystallization converts the *trans* to the *cis* isomer which is then isolated as a single diastereomer in a combined 76% yield from **12**. To set the stage for cyclization to the 7-azabicyclo[2.2.1]heptane, reduction to the *trans* amidoalcohol **14** is required. Sodium borohydride in methanol at 0° gives a gratifying 67% yield of the desired alcohol **14**, mp 180°, $[\alpha]_D^{23}$ -34.9 (c = 0.60, CH_2Cl_2). In addition, a 29% yield of the *cis* amidoalcohol, mp 195-6°, $[\alpha]_D^{23}$ -111.7 (c = 0.50, CH_2Cl_2), is also isolated.[14,15] Since the latter can be converted to the former, clearly the net yield of **14** can be improved. However, it was quite satisfactory for our purposes.

The final ring closure utilizes a trans-annular cyclization.[16] The Boc-amide nicely differentiates the amino alcohol for O-mesylation. The crude mesylate is directly subjected to trifluoroacetolysis. The crude amino mesylate is heated at reflux in acetonitrile to produce (-)-epibatidine as white needles, mp 64°, $[\alpha]_D^{23}$ -6.2 (c = 0.42, $CHCl_2$), whose spectral properties match those recorded. We did not optimize the yield of this three step ring closing sequence. The fact that the final step is recorded to proceed in excess of 80%[15] and that formation of the mesylate is virtually quantitative, the more modest overall yield may derive from the removal of the Boc group. Opportunity to improve the yield for the sequence does appear to exist but time limitations precluded its pursual.

This asymmetric synthesis of (-)-epibatidine can equally be applied to a synthesis of its enantiomer by simply switching ligand to ***ent*-4** or **3**. The differentiated amino alcohol derivative **7** should serve as a valuable asymmetric template for the synthesis of numerous amine targets. Further defining the chemistry of this building block will allow its more extensive use and possibly streamline this current synthesis. Nevertheless, the current route represents a useful entry to enantiomerically pure 7-azabicyclo[2.2.1]heptanes without the need to effect resolutions.

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