Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3867–3871

TETRAHEDRON: *ASYMMETRY*

An asymmetric synthesis of the novel H_3 agonist (+)-(3*R*,4*R*)-3-(4-imidazolyl)-4-methylpyrrolidine dihydrochloride (Sch 50971)

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Received 30 August 2000; accepted 1 September 2000

Abstract

A short, high yielding, enantioselective synthesis of the novel H_3 agonist Sch 50971 **1** is described. The key enantiodifferentiating step is the 1,4-addition of a chiral *N*-propionyloxazolidinone to a nitroolefin.

1. Introduction

The histamine H_3 receptor is a presynaptic autoreceptor that controls the release of histamine as well as other neurotransmitters such as serotonin, noradrenaline and acetylcholine.[1] Although the therapeutic applications of agonists and antagonists of the H_3 receptor have yet to be fully elucidated, potential areas of interest include obesity, Alzheimer's disease, attention deficit/hyperactivity disorder, sleep related disorders, and migraine.[2,3] We recently described a new class of H_3 agonists exemplified by the chiral pyrrolidine (+)-(3*R*,4*R*)-3-(4-imidazolyl)-4-methylpyrrolidine, dihydrochloride (Sch 50971, **1**).[4] Compound **1** is a potent ligand in vitro (K_i (H_3) = 2.3 nM, pD_2 = 7.5) and in vivo (ED_{50} = 0.3 mg/kg) and is selective for the H_3 receptor over the H_1 and H_2 receptors (K_i (H_1)>10 000 nM, pD_2<4.0, ED_{50}>100 mg/kg; pD_2 (H_2)<3).[4,5] Furthermore, **1** is effective at potentiating pentobarbital-induced sleep in the guinea pig (ED_{40} = 7 mg/kg orally), a measure of the sedation profile of a compound.[6] Although the synthesis of **1** was previously reported,[4] we required a more practical route to **1** that would

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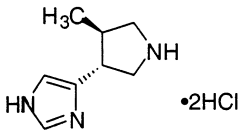
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00380-3

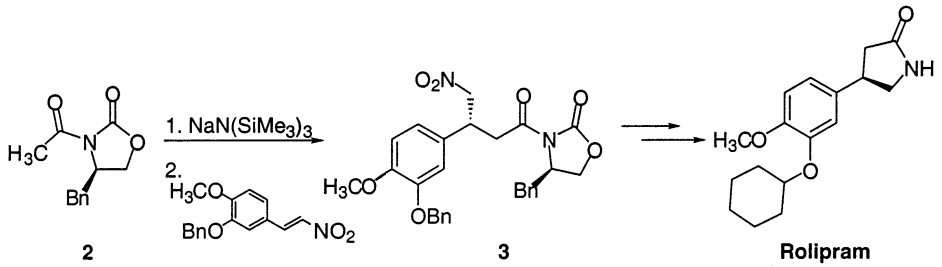
provide sufficient quantities of material to further define its biological and pharmacokinetic parameters. This paper describes an approach to the synthesis of **1** which utilizes the asymmetric Michael addition of a chiral acylated oxazolidinone to a substituted nitroolefin to set the required absolute stereochemistry at the adjacent chiral centers in **1**.



Sch 50971, 1

2. Chemistry

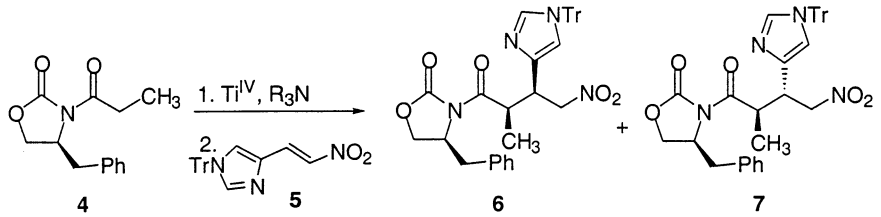
Compound **1** was initially obtained by resolution of its racemic di-*t*-Boc derivative using a Chiralcel OD column followed by removal of the Boc groups. Single-crystal X-ray analysis of this material demonstrated that **1** possesses the (3*R*,4*R*) configuration. Using this approach, we were able to obtain sufficient amounts of **1** for our preliminary biological investigations. However, chromatographic resolution was far from ideal for the synthesis of larger amounts of **1** since 50% of the material was lost in the resolution step. Therefore, we set out to develop a more efficient enantioselective approach to **1**. Chiral pyrrolidines are a common structural motif and, consequently, there are a number of approaches reported for their synthesis.[7] One method in particular seemed amenable to the problem at hand. Mulzer and co-workers found that addition of the sodium enolate of the chiral oxazolidinone **2** to a β-substituted nitroolefin proceeded with good diastereoselectivity (94:6) at the β-center to give the adduct **3** in 65% yield (Scheme 1).[8] This intermediate was further transformed into the chiral pyrrolidinone Rolipram.



Scheme 1.

The application of a similar strategy to our synthesis of **1** would involve the use of the chiral propionate oxazolidinone **4** thus requiring complete stereocontrol of both the α and the β stereogenic centers. In fact, Evans has shown excellent stereocontrol of the α center in chiral propionate additions to several Michael acceptors using $TiCl_3$(O*i*-Pr).[9] However, he reports this methodology did not show any control over the β stereogenic center in the addition to prochiral α,β-unsaturated ketones. Regardless, given the precedent for excellent control of the β center with nitroolefins with the Rolipram synthesis, we sought to investigate the feasibility of the Evans chiral propionate in the Michael addition to nitroolefins toward the preparation of **1**.

Our initial attempt at effecting the Michael reaction of oxazolidinone **4** with nitroolefin **5** utilized the conditions originally outlined by Evans and co-workers for the Michael addition of an oxazolidinone to an α,β-unsaturated ester, nitrile or ketone [Eq. (1), $TiCl_3$(O*i*-Pr), diisopropylethylamine (DIPEA), CH_2Cl_2].[9] Utilizing two equivalents of the enolate led to a reasonable chemical yield of the desired product **6** and moderate diastereoselectivity (entry 1, Table 1). A study was then undertaken in which the transition metal, ligand stoichiometry, temperature, and solvent conditions were varied to improve the diastereoselectivity of the reaction. Use of DMF as co-solvent ensured homogeneity of the reaction, but led to no addition product (entry 2). Use of other solvents and bases had a deleterious effect on the product yields (entries 3–6), while reversing the order of addition of $TiCl_4$, Ti(O*i*-Pr)$_4$, and oxazolidinone resulted in a less stereoselective reaction (entry 7). We next investigated the effect that the metal and ligand ratio had on the selectivity of the reaction. The boron enolate gave high diastereoselectivity with rather modest yields (entry 8). Varying the chloride:isopropoxide ratio on titanium from 4:0 to 3:1 to 1:1 suggested a trend toward greater diastereoselectivity with increasing number of isopropoxide ligands (entries 10, 1, 11). The maximum selectivity was obtained utilizing $TiCl_2$(O*i*-Pr)$_2$, which provided a 12:1 diastereomer ratio (entry 11). The optimum conditions determined by this study were the use of $TiCl_2$(O*i*-Pr)$_2$ at 4°C in CH_2C1_2, with DIPEA as base to give **6** and **7** in a 16:1 ratio and 77% yield (entry 13).[10] Purification of the crude material by crystallization from isopropanol/hexane raised the ratio of **6**:**7** to 22:1.



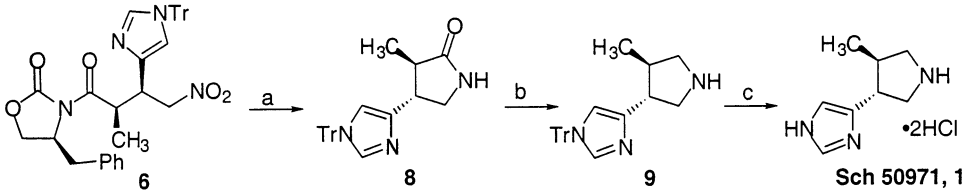
(1)

Table 1

Entry	Solvent	$TiCl_4$/Ti(O*i*-Pr)$_4$	Temp.	R_3N[a]	% Yield	**6**:**7**[b]
1	CH_2Cl_2	3:1	0°C→rt	DIPEA	77	6:1
2	CH_2Cl_2/DMF	3:1	0°C→rt	DIPEA	0	–
3	DME	3:1	0°C→rt	DIPEA	0	–
4	C_6H_5Cl	3:1	0°C→rt	DIPEA	5	6:1
5	$CHCl_3$	3:1	0°C→rt	DIPEA	0	–
6	CH_2Cl_2	3:1	0°C→rt	TEA	49	5:1
7	CH_2Cl_2	3:1[c]	0°C→rt	DIPEA	50	3:2
8	CH_2Cl_2	BBu_2Tf	0°C→rt	DIPEA	33	10:1
9	CH_2Cl_2	3:1	0→15°C	DIPEA	75	9:1
10	CH_2Cl_2	4:0	0°C→rt	DIPEA	80	3:2
11	CH_2Cl_2	1:1	0°C→rt	DIPEA	76	12:1
12	CH_2Cl_2	1:3	0°C→rt	DIPEA	10	–
13	CH_2Cl_2	1:1	0→4°C	DIPEA	77	16:1

[a] DIPEA = diisopropylethylamine, TEA = triethylamine.
[b] Product ratios were determined by HPLC and NMR.
[c] Inverse addition.

The completion of the asymmetric synthesis of **1** is given in Scheme 2. The Michael product **6** was reductively cyclized with no change in the diastereomer ratio to give compound **8** in 72% yield. Although reduction of the lactam could be accomplished by a number of different reagents such as LAH, RedAl, borane–methyl sulfide, or borane–methyl sulfide/$BF_3{\cdot}Et_2O$, LAH was the most effective giving **9** in 88% yield. Deprotection of **9** gave **1** as a hygroscopic white powder in 69% yield after crystallization from isopropanol/hexane.[11]



Scheme 2. (a) Ra-Ni, H_2, EtOH, 72%; (b) LAH, THF, 88%; (c) 4N HCl, 69%

3. Conclusion

In conclusion, we have found that Evans' chiral propionate derivatives give excellent enantioselective and diastereoselective control in the addition to nitroolefins. The application of this methodology toward preparing the novel H_3 agonist **1** resulted in the development of a practical, high yielding synthesis which has allowed for the production of over 0.6 kg of **1** to support preclinical and toxicological studies.

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10. A typical procedure is as follows: $TiCl_4$ (1.3 mol, 143 mL) was added dropwise to an ice-cold solution of $Ti(O\textit{i}\text{-}Pr)_4$ (1.3 mol, 387 mL) in methylene chloride (4 L). After stirring for 1 hour at this temperature, there was sequentially added diisopropylamine (2.6 mol, 453 mL), a solution of **4** (2.6 mol, 606 g) in methylene chloride (1.4

L), and a solution of **5** (1.3 mol, 497 g) in methylene chloride (7 L). After stirring overnight at 0–7°C, the reaction was quenched by the addition of glacial acetic acid (890 mL) and warmed to room temperature over 3 hours. Water (14 L) was added and the organic layer was separated. The aqueous layer was extracted a further two times with methylene chloride (500 mL each). The combined organic layers were washed sequentially with water (10 L), saturated aqueous sodium bicarbonate (5 L), and brine (5 L). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give an oil which was crystallized from 1:1 hexane:ethyl acetate to give compound **6** (488 g) as a white solid. The mother liquor from the crystallization was passed through a silica plug (load, 2:1; 10→50% EtOAc/hexane) and crystallized as above to give additional **6** (113 g, total yield 601 g, 75%). M.p. 82–92°C; IR (film) 1735, 1700, 1550, 1390, 1245 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 7.47–7.26 (15H, m), 7.10–7.07 (6H, m), 6.86 (1H, d, $J=1.3$ Hz), 4.95 (1H, dd, $J=10.2$, 12.4 Hz), 4.84 (1H, dd, $J=4.5$, 12.5 Hz), 4.71–4.67 (1H, m), 4.35 (1H, t, $J=8.4$ Hz), 4.20 (1H, dd, $J=3.1$, 8.8 Hz), 4.08 (1H, p, $J=7.0$ Hz), 3.90–3.86 (1H, m), 3.09 (1H, dd, $J=3.3$, 10.1 Hz), 2.81 (1H, dd, $J=8.8$, 13.8 Hz), 2.57 (1H, p, $J=1.8$ Hz), 1.06 (3H, d, $J=7.0$ Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 174.971, 152.880, 142.204, 139.033, 136.874, 135.349, 129.673, 129.362, 128.933, 128.061, 128.049, 127.310, 120.238, 77.489, 75.293, 66.165, 55.463, 40.211, 39.540, 38.015, 15.563; HRMS [FAB] calcd for $C_{37}H_{35}O_5N_4$ $[M+H]^+=615.2607$; found 615.2626; $[\alpha]_D^{25}=-46.7$ ($c=0.5$, MeOH).

11. Analytical data for compound **1**: ^1H NMR (300 MHz, CD_3OD) δ 8.96 (s, 1H), 7.66 (s, 1H), 4.9 (br s, 4 H), 3.84 (dd, $J_1=11$ Hz, $J_2=7.2$ Hz, 1H), 3.70 (dd, $J_1=11$ Hz, $J_2=7.8$ Hz, 1H), 3.4 (m, 2H), 3.1 (t, $J=11$ Hz, 1H), 2.6 (m, 1H), 1.2 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 135.732, 131.988, 117.840, 52.320, 50.362, 42.205, 40.081, 14.889. LRMS [electrospray] $m/z=152$ $[M+H]^+$; anal. calcd for $C_8H_{15}Cl_2N_3\cdot 0.6H_2O$: C, 40.90; H, 6.95; N, 17.89; found: C, 40.93; H, 6.90; N, 17.62; $[\alpha]_D^{25}=+43.5$ ($c=0.34$, MeOH).