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Asymmetric synthesis of (+)-(3a*S*,4*S*,7a*S*)-3a-hydroxy-4,7a-dimethylperhydroindane-1,5-dione

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Abstract: The asymmetric synthesis of the building block 3a-hydroxy-4,7a-dimethylperhydroindane-1,5-dione **3**, has been achieved from the triketone **4**. The use of additional amounts of base and heating increases the rate of the cyclization reaction catalyzed by *S*-(−)-proline, which is completed in less than 2 days. © 1997 Elsevier Science Ltd

During the synthesis of simple analogues of cardenolides, we explored the preparation of several perhydroindanyl derivatives. As the starting material we have employed the Hajos–Parrish ketone **1**,[1] readily available from stereospecific cyclization of triketone **2** by *S*-(−)-proline. We also described the required one carbon elongation of **1** at C-1[2] and the synthesis of several derivatives in this series.[3,4]

For the preparation of other families of analogues, carrying a 4α-methyl group, we used the same methodology to synthesize diketone **3**, starting from triketone **4**. In this case the method reported by Hajos and Parrish was very slow[5] (Table 1, entries 1 and 2).

2 **1** **4** **3**

In consequence, we decided to reinvestigate the procedure in order to prepare the chiral building block **3** of interest, in enantiomeric excess and yield comparable to those observed in the synthesis of **1**. For the latter, several studies on the enantioselective cyclization have been directed to changing the chiral catalyst[6] and other reaction conditions[5], finally leading to the procedure[7] employed in the asymmetric synthesis of different kinds of compounds.[8] Recently, the "neat" methodology has been used,[9] but the results and conditions are similar to those described by Hajos and Parrish twenty years ago. The reaction has also been studied in order to elucidate the mechanism and explain the high stereoselection observed, resulting in a mechanistic proposal (Figure 1) involving two molecules of *S*-(−)-proline in the rate limiting step of the reaction.[10] No further studies on the synthesis of **3** have been carried out.

In order to accelerate the cyclization, we decided to change two parameters: the temperature and the inclusion of an added base. Temperature increase would reduce the reaction time, but temperatures higher than 60°C yield side products. The added base is necessary for hydrogen bonding to the proton responsible of the stereoselection, linking the nitrogen atom of the proline and the oxygen atom of the carbonyl group (Figure 1) in the Agami's proposal; thus the electron pair of the proline nitrogen is then available for the cyclization. In the absence of added base, the proton is taken by a second molecule of proline, reflected by the order two in proline deduced from the kinetic studies of the reaction rate[10]. The base must be selected to avoid faster reaction processes, which can lead to non-enantioselective cyclization if the added base is a better catalyst than proline. Furthermore, the base can produce other

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Table 1. (a) Total base added (Base/Pro: mol/mol) and time (hr). (b) By *, ^{1}H-NMR or by #, GC. (c) By chromatography. (d) Calculated e.e. referred to $[\alpha]_D$ of recrystallized **3**, entry 13. Compound **3** $[\alpha]_D$ lit.[5]: +34.6. The enantiomeric purity of this compound was checked by ^{1}H-NMR using a lanthanide chiral shift reagent

	%mol S-(-)-Pro/ Substrate	Base	Temp. °C	INITIAL Base/Pro (mol/mol) Time hours	EVOLUTION Base/Pro (mol/mol) Time hours	Total (a) Base/Pro Time	Transfor mation (%) (b)	3 (%) (b)	Isol. 3 % (c)	$[\alpha]_D$ (e.e.) (d)	Side Product
1	4.5	---	r.t.	--- 297		--- 297	25 *	25 *			
2	6.0	---	60°	--- 120		--- 120	74* #	48* #	38.7	+32.3 (93)	
3	6.0	KOH	60°	-- 48	1.0 (2 times) = every 132h	2.0 312	81 #	58 #	54.3	+20.0 (58)	
4	20.0	BuLi	60°	0.6 24		0.6 24	95 *	50 *	40.0	+20.0 (58)	5
5	6.0	BuLi	60°	-- 48	0.4 (3 times) = every 8h	1.2 74	71 #	46 #	45.2	+17.9 (52)	5
6	---	Piperi dine	r.t.	50% (substrate) 8		50%(subs) 8	100 *	90 *	67.0	racem.	
7	6.0	Piperi dine	60°	0.6 96		0.6 96	54 * #	34 * #			
8	6.0	Piperi dine	60°	-- 24	1.0 (6 times) = every 16h	6.0 120	88 #	61 #	50.2	+32.5 (94)	
9	6.0	Piperi dine	60°	-- 24	0.8 (3 times) = every 45h	2.5 159	94 #	72 #	70.0	+30.7 (88)	
10	20.0	Piperi dine	60°	--- 24	1.0 (5 times) = every 13h	5.0 90	95 #	48 #	27.2	+24.8 (72)	6
11	6.0	Piperi dine	60°	--- 23	0.33 (15 times) = every 5h	4.95 98	92 #	66 #	40.5		6
12	6.0	Piperi dine	60°	--- 2	0.25 (32 times) = every 2h	8.0 70	86 #	60 #	45.3		6
13	6.0	Piperi dine	60°	--- 2	0.25 (22 times) = every 1.5h	5.5 35	94 #	65 #	50.3	+34.7 (100)	6

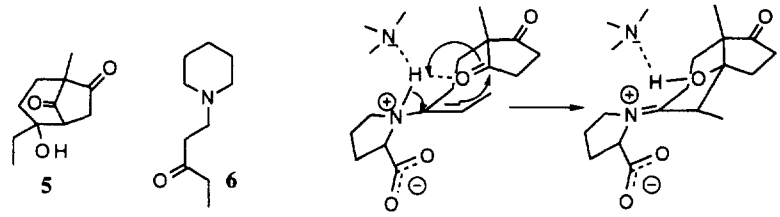

Figure 1. Proposed mechanism for the stereoselective cyclization of triketones to perhydroindanediones.

competitive reactions, as cyclization to bicyclic diketones **5**.[1] Our studies are summarized in Table 1, showing the effect of both factors on the reaction time, appearance of side products **5** or **6** and the enantiomeric excess obtained in the isolated product **3**.[11]

The increase of temperature in the absence of added base (entries 1 and 2) reduces the reaction time to five days. The addition of strong bases completes the second step of the reaction (entries 3–5), but the proline is transformed into prolinate without the proton required for the enantioselective process; furthermore, the enantiomeric excess decreases and side product **5** is obtained. The addition of a nitrogen base (piperidine) increases the rate of the reaction when the initial evolution slows (entries 8 and 9), but tertiary amine (triethylamine) has no effect. The addition of piperidine must be in small amounts after an initial period of time only with proline, to avoid racemization (entry 6) and reduce the appearance of side product **6** (entry 10). The added piperidine can also contribute to the recovery of the catalytic *S*-(−)-proline from the cyclization product, given that the reaction stops if no further base is added (entry 7). After optimization, the addition of piperidine in small amounts (0.25:1 piperidine:proline) every 1–2 hours after 2 initial hours only with proline, produces very good results in less than 2 days.

This procedure yields diketone **3** in very good e.e., and can be applied to the enantioselective cyclization of other interesting building blocks in the synthesis of perhydroindanes, steroid analogues and other molecules. In conclusion, the addition of a non-chiral base to the *S*-(−)-proline catalyzed cyclization has proved to be very effective, increasing the reaction of the enantioselective process.

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References

1. Z.G. Hajos and D.R. Parrish *J. Org. Chem.* **1974**, *39*, 1612–1615; 1615–1621.
2. M. Medarde; E. Caballero; F. Tomé; P.G. Gracia; M. Boya and A. San Feliciano *Synt. Commun.* **1995**, *25*, 1377–1382.
3. M. Medarde; F. Tomé; J.L. López; E. Caballero; M. Boya; C.P. Melero and A. San Feliciano *Tetrahedron Lett.* **1994**, *35*, 8683–8686.
4. M. Medarde; E. Caballero; F. Tomé; C.P. Melero; M. Boya and A. San Feliciano *An. Quim.* **1995**, *91*, 89–94.
5. Z.G. Hajos and D.R. Parrish **1976** *US.Pat.* **3,975,440** and **3,975,442**.
6. S. Danishesfky and P. Cain *J. Am. Chem. Soc.* **1976**, *98*, 4975–4982. P. Buchschacher; J.-M. Cassal; A. Fürst and W. Meier *Helv. Chim. Acta* **1977**, *60*, 2747–2755. U. Eder; G. Sauer and R. Wiechert *Angew. Chem.* **1971**, *83*, 492–493. J. Martens and S. Lübben *Arch. Pharm.* **1991**, *324*, 59–60.
7. Z.G. Hajos and D.R. Parrish *Org. Synth.* **1984**, *63*, 26–30.
8. I. Shimizu; Y. Naito and J. Tsuji *Tetrahedron Lett.* **1980**, *21*, 487–490. R.A. Micheli; Z.G. Hajos; N. Cohen; D.R. Parrish; L.A. Portland; W. Sciamanna; M.A. Scott and P.A. Wehrli *J. Org. Chem.* **1975**, *40*, 675–681. G. Sauer; U. Eder; G. Haffer; G. Neef and R. Wiechert *Angew. Chem. Int. Ed.* **1975**, *14*, 417.
9. D. Rajagopal; K. Rajagopalan and S. Swaminathan *Tetrahedron Asymmetry* **1996**, *7*, 2189–2190.
10. C. Agami; C. Puchot and H. Sevestre *Tetrahedron Lett.* **1986**, *27*, 1501–1504. C. Agami; F. Meynier; C. Puchot; J. Guilhem and C.Pascard *Tetrahedron* **1984**, *40*, 1031–1038. C. Agami *Bull. Soc. Chim. Fr.* **1988**, 499–507.
11. ^{1}H-NMR (200 MHz; $CDCl_3$): 1.15 (d, J=6.8 Hz; Me-9), 1.32 (s; Me-8), 2.72 (q, J=6.8 Hz; H-4). ^{13}C-NMR (200 MHz; $CDCl_3$): 219.2(1), 28.3(2), 36.4(3), 84.5(3a), 50.9(4), 209.6(5), 29.8(6), 32.7(7), 53.6(7a), 12.5(8), 6.7(9). Relative stereochemistry at C-4 established by the nOe observed at H-4 upon irradiation of Me-8.

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