Pergamon

Tetrahedron Letters 39 (1998) 4151–4154

TETRAHEDRON LETTERS

A Solution-Phase Combinatorial Parallel Synthesis of 3β-Amido-3α-hydroxy-5α-androstane-17-ones

René Maltais and Donald Poirier*

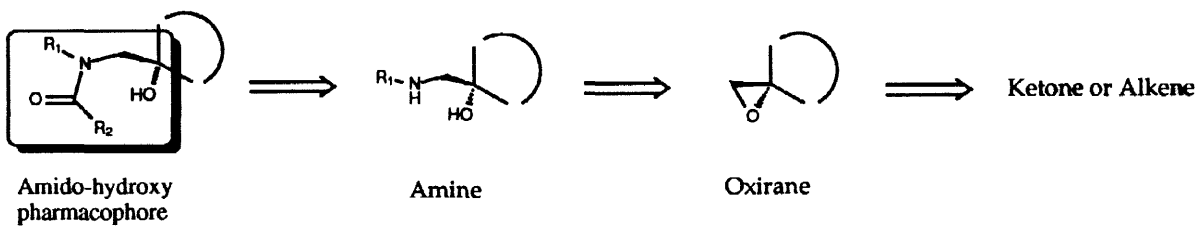
Medicinal Chemistry Division of LREM
CHUL Research Center and Laval University
2705 Laurier Boulevard
Québec, QC, CANADA G1V 4G2

Received 6 February 1998; accepted 8 April 1998

Abstract: A two-level library of 3β-amido-3α-hydroxy-5α-androstane-17-one compounds was synthesized from a steroid precursor using the solution-phase parallel synthesis. The compounds were easily obtained in high purity by regioselective aminolysis of the oxirane intermediate followed by acylation of the amine. Since oxiranes can be generated from readily available ketones or alkenes, the proposed strategy give access to a large series of compounds.

Parallel combinatorial chemistry is an efficient approach for the rapid generation of libraries of compounds.[1-3] Until recently, these libraries have been synthesized mainly on a solid support.[4-6] Parallel solution-phase synthesis is a very interesting alternative approach to solid support synthesis.[7-18] Validation time, facility of manipulations and the diversity of reactions that can be performed are some of the advantages that characterize solution-phase synthesis.

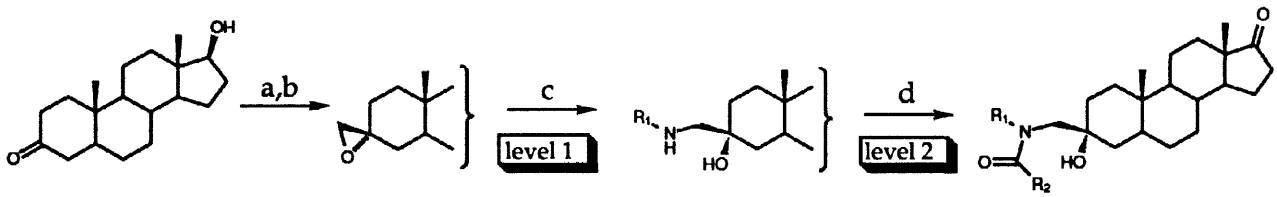
Although the generation of amido-hydroxy pharmacophore (Scheme 1) is suitable to solution phase parallel synthesis, this approach has not been previously described. To validate the strategy, we first chose a steroid backbone as substrate to stereoselectively generate the oxirane that would be the precursor of the 3β-substituted-3α-hydroxy pharmacophore. With a reactivity that is generally lower than that of smaller molecules, steroids are an ideal substrate to show the versatility and limitation of this methodology. In this letter, we report the preparation of a twenty-member library of 3β-amido-3α-hydroxy-5α-androstane-17-ones generated from an oxirane system by a two levels solution phase parallel synthesis (Scheme 2).



Scheme 1. Retrosynthetic synthesis of an amido-hydroxy pharmacophore.

0040-4039/98/$19.00
PII: S0040-4039(98)00772-2

The stereoselective reaction of dihydrotestosterone (**1**) with dimethylsulfoxonium methylide[19] followed by an oxidation of 17β-OH using TPAP[20] gave the spiro-3(*R*)-[oxirane-2',5α-androstan]-17-one (**2**) in good yield (70%) as the steroid precursor of the library (Scheme 2). A strategy using two levels of reactions was thereafter investigated to generate the library. The first level of reactions consisted of opening regioselectively the oxirane **2** by a series of primary aliphatic amines (propyl, amyl, octyl, benzylamine) to obtain four sets of secondary amines **3** distributed in twenty different vials. The second level of reactions consisted of adding regioselectively an aliphatic acyl chlorides (propanoyl, pentanoyl, octanoyl or benzoyl chloride) to each set of different secondary amines **3** to give the corresponding amides **4** (Table 1).

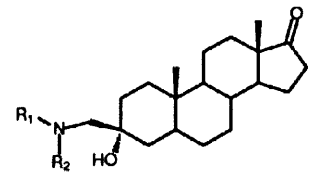


Scheme 2. Synthesis of a 3β-amido 3α-hydroxy steroidal library (compounds **4**). The reagents are: a) NaH, Me_3SOI, DMSO, 50°C; b) TPAP, NMO, molecular sieves, CH_2Cl_2, rt; c) R_1NH_2, $LiClO_4$, CH_3CN, 55°C; d) R_2COCl, pyridine, CH_2Cl_2, rt.

The conditions used for the two reaction levels were first optimized on some individual target compounds of the library. For the aminolysis (level 1), the addition of lithium perchlorate[21] (2.0 eq) and appropriate amine (1.0 eq) to oxirane **2** (30 mg, 0.1 mmol) in refluxing anhydrous acetonitrile for 7 days, gave the highest yield of the corresponding amine **3**. As work-up, the acetonitrile solution was evaporated under vacuum with a speedvac apparatus (Juan RC1010). The crude product was dissolved in ethyl acetate, washed with water and then purified by fast filtration on silica gel.[22] For the amidation (level 2), the appropriate acyl chloride (1.0 eq) was added to secondary amine **3** in the presence of pyridine (2.0 eq) and dichloromethane (4 mL). After 3 hours at room temperature, the dichloromethane was removed under vacuum (speedvac apparatus) and ethyl acetate was added. The purification of level 2 was done using a two step procedure: *1*) a basic aqueous work-up (NaOH 40%) to remove the carboxylic acid by-product as well as to release pyridine from HCl salt, and *2*) a fast silica gel filtration.[23]

All library members were characterized by ^1H NMR and high resolution mass spectra. Futhermore, compounds **12** and **15** were fully characterized by IR, ^1H NMR, ^{13}C NMR and high resolution mass spectra. Their purities were also determined by HPLC and found to be high (85-98%) except for four benzoyl derivatives (50-66%) (Table 1). To improve the purities of benzoyl derivatives (**9**, **14**, **19**, **24**), two strategies were tested. In the first, the benzoic acid by-product, responsible for low purities, was decreased by using 0.8 eq of benzoyl chloride rather than 1.0 eq. With this small modification, the purities of benzoyl derivatives were increased to 81-88%. The second strategy use the recently reported Complementary Molecular Reactivity and Molecular Recognition technology (CMR/R).[17-18] Thus a complementary amino resin was successfully used to remove unreacted benzoyl chloride giving purities of 86-93% for benzoyl derivatives. Since the purities of benzoyl series were greatly increased using one of both strategies reported above, very high purities are now associated with all library members (93% average).

Table 1. Structure and analytical data of a 20-member library[a]



Compound	R_1	R_2	Yield %[b]	Purity %[c]	m/z[d]
5		H	n.a.	92	362.3067 (362.3059)
6			44	96	432.3468 (432.3478)
7			40	97	460.3777 (460.3791)
8			48	94	502.4245 (502.4260)
9			54	66; 81; 93 [e]	466.3300 (466.3281)
10		H	n.a.	97	390.3386 (390.3372)
11			49	94	460.3777 (460.3791)
12			60	94	488.4098 (488.4104)
13			71	93	530.4556 (530.4573)
14			61	65; 88; 96 [e]	494.3620 (494.3634)
15		H	n.a.	98	432.3846 (432.3842)
16			42	98	502.4245 (502.4260)
17			45	94	530.4550 (530.4573)
18			54	85	572.5054 (572.5042)
19			43	50; 88; 89 [e]	536.4114 (536.4104)
20		H	n.a.	94	410.3077 (410.3059)
21			60	88	480.3465 (480.3478)
22			44	88	508.3775 (508.3791)
23			36	91	550.4244 (550.4260)
24			69	63; 84; 86 [e]	514.3314 (514.3321)

a) This library was achieved in 10 days (8 days of reaction and 2 days of purification) by one worker.
b) Yields refer to percentage of product recovered after the last purification procedure.
c) Product purities were determined by analytical HPLC using μPorasil column (hexane / isopropanol) or a Nova~Pack, C18 column (MeOH / H_2O / CH_3CN) for amines and amides, respectively.
d) m/z refer to $[M+H]^+$, calculated values are given in parentheses.
e) Yields respectively for *1*) ArCOCl (1.0 eq); 2) ArCOCl (0.8 eq); *3*) ArCOCl (1.0 eq) with amino-resin treatment. A silica gel filtration was performed in all cases.

In summary, we have developed a strategy to quickly generate a library of 3β-amido-3α-hydroxy-5α-androstane-17-ones with high purity by solution-phase parallel chemistry. Our first 20-member steroidal library was designed as a model for the development of a more voluminous library. The great number of primary amines and acyl chlorides (or acid precursors) commercially available give access to such voluminous libraries. The strategy is also useful for the steroidal oxiranes derived from other keto steroids. More importantly, the strategy will be applicable to a wide variety of non-steroidal molecules possessing a ketone or an alkene to generate the key oxirane intermediate. Futhermore, these libraries of amido-hydroxy compounds have the potential to serve as probes for SAR information quest on different therapeutic targets. In this perspective, a 200-member library of steroidal 3β-amido-3α-hydroxy compounds is presently under development by our group.

Acknowledgments: We thank the Medical Research Council of Canada (MRC) for their financial support through an operating grant, the Laboratory of Molecular Endocrinology (Dr. F. Labrie, Director) for providing the chemical facilities, and the Chromatographic Analysis Unit for HPLC.

References and Notes

1. Wilson, S.R.; Czarnik, W.A. *Combinatorial Chemistry: Synthesis and Application*, John Wiley: New-York, 1997; pp. 269.
2. Günther J. *Combinatorial Peptide and Nonpeptide Libraries*, VCH: Weinheim, 1996; pp. 544.
3. Terrett, N.K.; Gardner,M.; Gordon, D.W.; Kobylecki, R.J.; Steele, J. *Tetrahedron.* **1995**, *51*, 8135-8173
4. Bristol, J.A. *Tetrahedron* **1997**, *53*, 6573-6705.
5. Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron.* **1996**, *52*, 4527-4554.
6. Xiao, X.Y.; Parandoosh, Z.; Nova, M.P. *J. Org. Chem.* **1997**, *62*, 6029-6033.
7. Boger, D.L.; Tarby, C.M.; Myers, P.L.; Caporale, L.H. *J. Am. Chem. Soc.* **1996**, *118*, 2109-2110.
8. Curran, D.P.; Hoshino, M. *J. Org. Chem.* **1996**, *61*, 6480-6481.
9. An, H.; Cook, P.D. *Tetrahedron Lett.* **1996**, *37*, 7233-7236.
10. Gayo, L.M.; Suto, M.J. *Tetrahedron Lett.* **1997**, *38*, 513-516.
11. Cheng, S.; Tarby, C.M.; Comer, D.D.; Williams, J.P.; Caporale, L.H.; Myers, P.L.; Boger, D.L. *Bioorg. Med. Chem.* **1996**, *4*, 727-737.
12. Pirrung, M.C.; Chen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240-1245.
13. Chg, B.L.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1997**, *12*, 1511-1514.
14. Booth, J.R.; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886.
15. Shuker, J.A.; Siegel, M.G.; Matthews, D.P.; Weigel, L.O. *Tetrahedron Lett.***1997**, *38*, 6149-6152
16. Kaldor, S.W.; Siegel, M.G.; Fritz, J.E.; Dressman, B.A.; Hahn, P.J. *Tetrahedron Lett.***1996**, *37*, 7193-7196.
17. Flynn, D.L.; Crich, J.Z.; Devraj, R.V.; Hockerman, S.L.; Parlow, J.J.; South, M.S.; Woodard, S.S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4881.
18. Parlow, J.J.; Mischke, D.A.; Woodard, S.S. *J. Org. Chem.* **1997**, *62*, 5908-5919.
19. Cook, C.E.; Corley, R.C.; Wall, M.E. *J. Org. Chem.* **1968**, *38*, 2789-2793.
20. Griffith, P.; Ley, S.V. *Aldrichimica Acta.* **1990**, *23*, 13-21.
21. Chini, M.; Crotti, P.; Macchia, F.J. *J. Org. Chem.* **1991**, *56*, 5939-5942.
22. Typically, 30 mg of amine **3** was added to a 10 mL syringe loaded with silica gel (2 mL) and the compound was eluted using 3 mL of hexane / ethyl acetate (1:1) followed by 5 mL of chloroform / methanol (9:1).
23. Same procedure as *note 22* except that 10 mL of hexane / ethyl acetate (8:2) was used as eluent.