Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1449–1453

TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiomerically pure 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones via enzymatic resolution: preparation of the antihypertensive agent (*R*)-SQ 32926†

Barbara Schnell, Ulrike T. Strauss, Petra Verdino, Kurt Faber and C. Oliver Kappe*

Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Received 16 December 1999; accepted 28 February 2000

Abstract

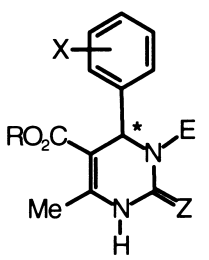
A practical and short synthesis of the enantiomerically pure dihydropyrimidone antihypertensive agent (*R*)-SQ 32926 has been developed. The key step in the synthesis is the enzymatic resolution of an *N*3-acetoxymethyl-activated dihydropyrimidone precursor by *Thermomyces lanuginosus* lipase. The absolute configuration of (*R*)-SQ 32926 was confirmed by circular dichroism spectroscopy. © 2000 Elsevier Science Ltd. All rights reserved.

4-Aryl-3,4-dihydro-2(1*H*)-pyrimidone esters of type **1** (DHPMs) represent a heterocyclic system of remarkable pharmacological efficacy.[1–11] In recent years, appropriately functionalized derivatives have emerged as, e.g., calcium channel modulators,[2] α_{1a}-adrenoceptor-selective antagonists,[3] mitotic kinesin Eg5 inhibitors,[4] and neuropeptide Y (NPY) antagonists.[5] Close structural analogs derived from **1** have been reported as effective antiviral (hepatatis B) agents[6] and as group 2 metabotropic glutamate receptor antagonists.[7] Of particular importance are the *N*3-acyl substituted analogs SQ 32926 **2**[8] and SQ 32547 **3**[9] which have been identified as potent orally active antihypertensive agents.[8–10] These substances can be considered as close structural analogs of the therapeutically widely used calcium channel blockers of the 1,4-dihydropyridine type (DHPs, e.g. nifedipine, amlodipine, nilvadipine).

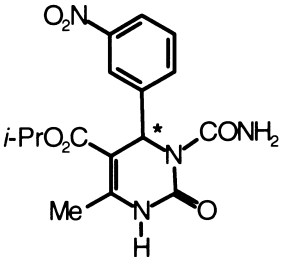
* Corresponding author. Fax: +43-316-3809840; e-mail: oliver.kappe@kfunigraz.ac.at

† Synthesis and reactions of Biginelli compounds, part 20; for part 19, see: Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, *56*, 1859–1862.

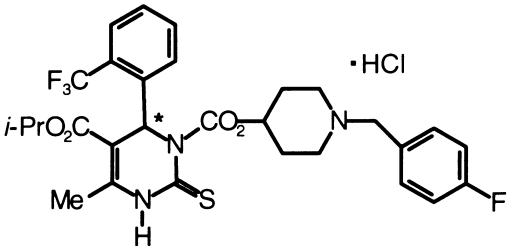
PII: S0957-4166(00)00081-1



1, R = alkyl, Z = O, S
X = NO_2, CF_3, OH, F
E = H, ester, amide



2, SQ 32926

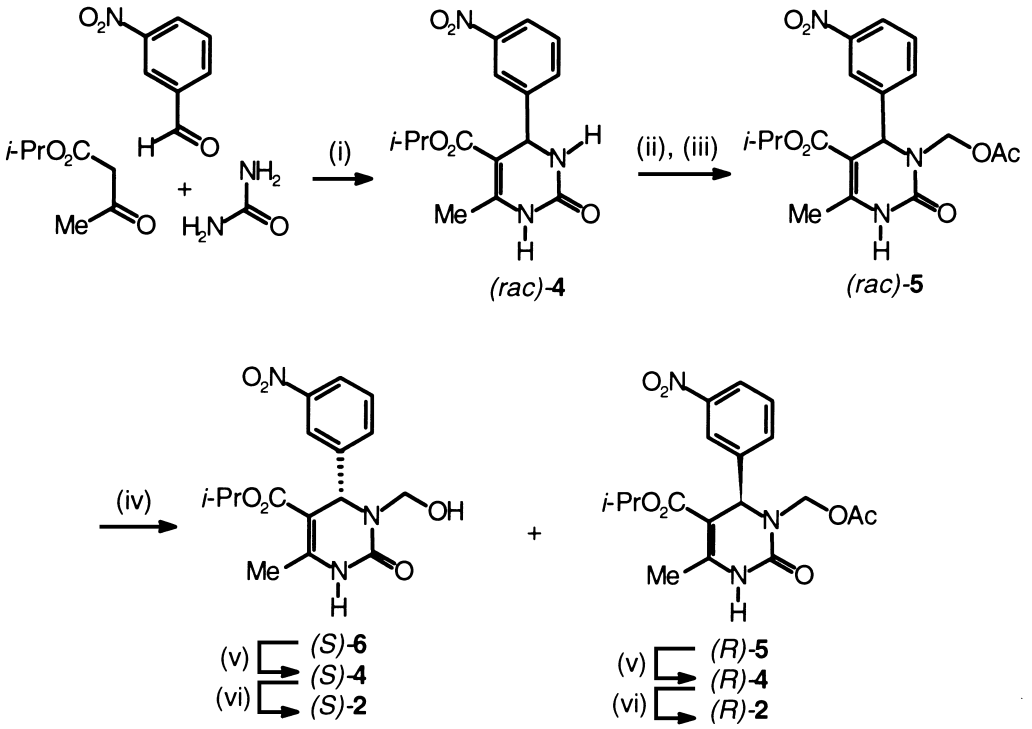


3, SQ 32547

DHPMs of type **1** are inherently asymmetric molecules and the influence of the absolute configuration at the stereogenic center at C4(*) on molecular activity is well documented.[11] In SQ 32926 **2**, for example, it is exclusively the (*R*)-enantiomer that carries the therapeutically desired antihypertensive effect.[8] Access to enantiomerically pure DHPMs is therefore a prerequisite for the development of useful drugs of this structural type. In the absence of any known asymmetric synthesis for this heterocyclic target system we became interested in obtaining enantiomerically pure DHPM analogs via a chemoenzymatic synthesis. In the past, enantiomerically pure DHPMs were obtained by classical resolution of the corresponding racemic carboxylic acids,[12] by separation of diastereomeric derivatives bearing chiral auxiliaries at *N*3,[2,3,8,9] or by enantioselective HPLC.[13,14]

Herein we report the first application of a lipase-catalyzed kinetic resolution for the gram-scale synthesis of enantiomerically pure DHPMs.[15] The usefulness of the method is further demonstrated by the synthesis of the antihypertensive agent (*R*)-SQ 32926.

Our strategy towards enantiomerically pure DHPMs (e.g. SQ 32926) is outlined in Scheme 1. Racemic DHPM precursor **4** was available in 94% yield by Biginelli three-component cyclocondensation of isopropyl acetoacetate, 3-nitrobenzaldehyde and urea, using polyphosphate ester (PPE) as reaction mediator.[16] An enzymatically cleavable ester functionality was readily introduced in proximity to the C4 stereogenic center at *N*3 by hydroxymethylation with formaldehyde, followed by standard acetylation with acetyl chloride.[17] The resulting *N*3-acetoxymethyl activated DHPM (*rac*)-**6** was obtained in ca. 80% overall yield and high purity from **4** as a single regioisomer (no *N*1- or bis-functionalized products could be detected). Enantioselective enzymatic hydrolyses of (*rac*)-**6** were carried out in diisopropyl ether/phosphate buffer (pH 7.0) mixtures at room temperature. After screening a set of commonly used lipases, *Thermomyces lanuginosus* (Amano CE lipase) was identified as the biocatalyst of choice. Using dextran as



Scheme 1. Reagents and conditions: (i) polyphosphate ester, THF, reflux, 24 h; (ii) 37% CH_2O, EtOH, K_2CO_3, reflux, 48 h; (iii) AcCl, THF, Et_3N, 0°C, 1 h; (iv) lipase (see Ref. 19); (v) aq. NH_3 (concd), MeOH, rt, 48 h; (vi) CCl_3CO–NCO, THF, rt, 24 h; then MeOH, SiO_2, rt, 48 h

additive[18] excellent enantioselectivities ($E > 200$) were achieved in a highly reproducible manner. After 72 h at 23°C a 50:50 mixture of hydroxymethyl DHPM (*S*)-**6** (96% ee) and acetoxymethyl DHPM (*R*)-**5** (98% ee) was obtained after simple silica gel chromatography.[19] Upon treatment with ammonia in methanol[17] both products were degraded in good yield into the *N*3-unsubstituted derivatives (*S*)- and (*R*)-**4**, respectively, without any racemization. The desired target molecule (*R*)-**2** (SQ 32926) was finally obtained in one step from (*R*)-**4** by *N*3-carbamoylation with trichloroacetyl isocyanate.[20] The physical and spectral data of this material were in excellent agreement with literature values.[21] The enantiomeric excess of (*R*)-**2** was 98% based on chiral HPLC measurements (Whelk-O1, heptane:2-propanol 70:30). The biologically inactive enantiomer (*S*)-**2** was obtained in an analogous manner.

The absolute configurations of (*R*)- and (*S*)-**2** were confirmed by circular dichroism (CD) spectroscopy. Fig. 1 shows the CD spectra of both enantiomers of DHPM **2**. Based on comparsion with reference CD spectra of DHPMs with known absolute configuration[22] the enantiomer showing a positive Cotton effect at 288 nm was assigned the (*S*)-configuration. Comparison of the specific rotations for (*R*)- and (*S*)-**2** with reference literature data yielded identical/matching results.[21]

In conclusion we have developed a chemoenzymatic synthesis for enantiomerically pure dihydropyrimidine derivatives of type **1** that is based on a lipase-catalyzed kinetic resolution. Key to the success of this approach is the regioselective hydroxymethylation of dihydropyrimidones at *N*3, which allows the introduction of the enzymatically cleavable ester functionality. We anticipate

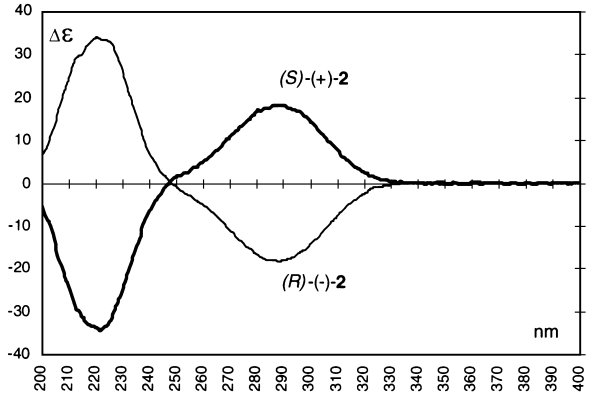


Figure 1. CD spectra of (*R*)- and (*S*)-**2** in methanol

that the methodology introduced herein can be employed for the resolution of a variety of other DHPM analogs, e.g. potential drug candidates.

Acknowledgements

This work was supported by the 'Jubiläumsfonds der Österreichischen Nationalbank' (Project 7904) and the Austrian Science Fund (FWF, Projects P-11994-CHE and F115). Amano Pharm. Co. is thanked for the generous donation of enzymes.

References

1. For a review on dihydropyrimidones of this type, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
2. Atwal, K. S.; Rovnyak, G. C.; Kimball, D. S.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629–2635.
3. Nagarathanm, D.; Miao, S. W.; Lagu, B.; Chiu, G.; Fang, J.; Dhar, T. G. M.; Zhang, J.; Tyagarajan, S.; Marzabadi, M. R.; Zhang, F. Q.; Wong, W. C.; Sun, W. Y.; Tian, D.; Wetzel, J. M.; Forray, C.; Chang, R. S. L.; Broten, T. P.; Ransom, R. W.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Kling, P.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Vyas, K. P.; Gluchowski, C. *J. Med. Chem.* **1999**, *42*, 4764–4777 and following papers in this series.
4. Mayer, T. U.; Kapoor, T. M.; Haggarty, S.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971–974.
5. Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT Int. Appl. WO 98 33,791; *Chem. Abstr.* **1998**, *129*, 148989g.
6. Goldmann, S.; Stoltefuß, J.; Paessens, A.; Graef, E.; Lottmann, S. Ger. Offen. DE 19,817,262; *Chem. Abstr.* **1999**, *131*, 286535y.
7. Wichmann, J.; Adam, G.; Kolczewski, S.; Mutel, V.; Woltering, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1573–1576.
8. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806–811.
9. Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254–3263.
10. Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289–294.
11. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119–129.

12. Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W. *Tetrahedron* **1992**, *48*, 5473–5480.
13. Kleidernigg, O. P.; Kappe, C. O. *Tetrahedron: Asymmetry* **1997**, *8*, 2057–2067.
14. Lewandowski, K.; Murer, P.; Svec, F.; Fréchet, J. M. J. *J. Comb. Chem.* **1999**, *1*, 105–112.
15. In the corresponding DHP series the application of biocatalytic methods in order to obtain enantiomerically pure derivatives is well established: (a) Holdgrün, X. K.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3465–3468. (b) Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Ebiike, H.; Achiwa, K. *Tetrahedron Lett.* **1992**, *33*, 7157–7160. (c) For a recent review, see: Marchalín, S.; Chudík, M.; Mastihuba, V.; Decroix, B. *Heterocycles* **1998**, *48*, 1943–1958.
16. Kappe, C. O.; Falsone, F. S. *Synlett* **1998**, 718–720.
17. Nagai, H.; Shiozawa, T.; Achiwa, K.; Terao, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1933–1938.
18. de la Casa, R. M.; Sánchez-Montero, J. M.; Sinisterra, J. V. *Biotechnol. Lett.* **1999**, *21*, 123–128.
19. A mixture of (*rac*)-**5** (200 mg) in diisopropyl ether (200 mL) and Amano CE lipase (400 mg, enzyme content 4–6%) in phosphate buffer (pH = 7, 35 mL) containing 5% dextran (*Leuconostoc mesenteroides*, MW 260 000) was shaken at 180 rpm at rt for 72 h (51% conversion). The organic layer was washed with water, dried, and concentrated in vacuo. Silica gel chromatography (ethyl acetate:hexane 2:1) provided (*R*)-**5** (R_f = 0.43, 90 mg, 90% yield, 98% ee) and (*S*)-**6** (R_f = 0.17, 88 mg, 99% yield, 96% ee). This protocol was peformed on a sixfold scale (1.20 g starting material) giving identical results. The amount of lipase can be significantly reduced; however, in this instance the reaction time is increased to ca. 5 d.
20. Alpegiani, M.; Bedeschi, A.; Giudici, F.; Perrone, E.; Visentin, G.; Zarini, F.; Franceschi, G. *Heterocycles* **1990**, *30*, 799–812.
21. Data for (*R*)-(–)-**2**: mp 161–164°C (lit.[8] mp 160–161°C); ^{1}H NMR (DMSO-d_6) 1.14 (d, J = 6.0 Hz, 3H), 1.24 (d, J = 6.0 Hz, 3H), 2.30 (s, 3H), 4.95 (m, J = 6.0 Hz, 1H), 6.58 (s, 1H), 7.58–7.70 (m, 3H), 8.08 (s, 1H), 8.10–8.22 (m, 2H), 10.20 (s, 1H); $[\alpha]_D$ = –136.7 (c = 1, MeOH) (lit.[8] $[\alpha]_D$ = –147.4 (c = 1, MeOH)).
22. Krenn, W.; Verdino, P.; Uray, G.; Faber, K.; Kappe, C. O. *Chirality* **1999**, *11*, 659–662.