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Synthesis of the Angiotensin-Converting Enzyme Inhibitor (±)-A58365A

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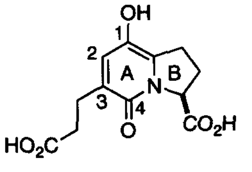
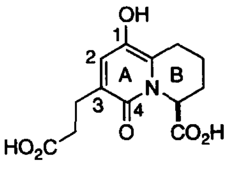
Abstract Crystalline (±)-A58365A (**1**), an inhibitor of angiotensin-converting enzyme, was synthesized by a process based on enyne radical cyclization (**13a,b** → **14a,b**). The starting material for this process was constructed by coupling the spiro lactone **6** with the amino acid **7**, followed by elaboration into **13a,b**. © 1998 Elsevier Science Ltd. All rights reserved.

The pyridone acids **1** and **2**, which were isolated in the Eli Lilly laboratories from the fermentation broth of the bacterium *Streptomyces chromofuscus*, and given the designations A58365A and A58365B, respectively, are inhibitors of angiotensin-converting enzyme.[1] This property makes them of potential value as lead compounds for the design of blood-pressure lowering drugs.

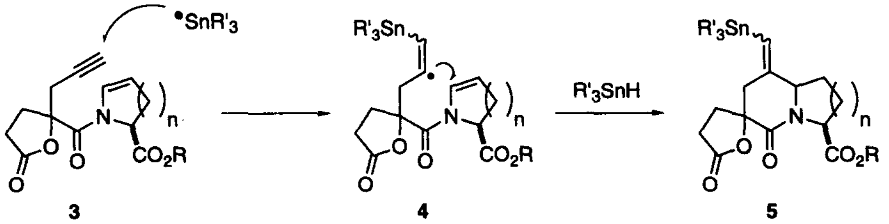


1



2

Racemic **2** was synthesized in this laboratory some time ago,[2] and we now report a synthesis of its congener **1**.[3] Our general approach to compounds of the bicyclic pyridone class involves, as the key step, a radical cyclization along the lines[4] summarized in Scheme 1 (**3** → **4** → **5**). Subsequent cleavage of the exocyclic carbon-carbon double bond in **5** serves to generate the C(1)[5] carbonyl (shown enolized in both **1** and



Scheme 1

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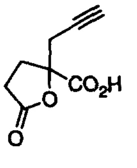
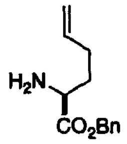
2), and treatment with a mild base then opens the spirolactone in a way (*cf.* Scheme 3, **16a,b** → **17**) that releases the side chain and introduces the C(2)-C(3) double bond. Application of this approach to the synthesis of **1**, required the subunits **6** and **7**. The former was available, as described previously,[2,6] and the latter was

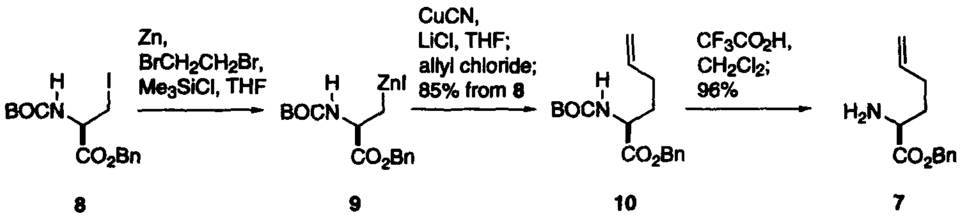


6



7

made from the iodide **8** by allylation[8] of the derived organozinc (Scheme 2, **8** → **9** → **10**), followed by deprotection (TFA, 96%, **10** → **7**). Coupling of **6** and **7** under standard conditions (EDCI,[12] HOBT, DMF;

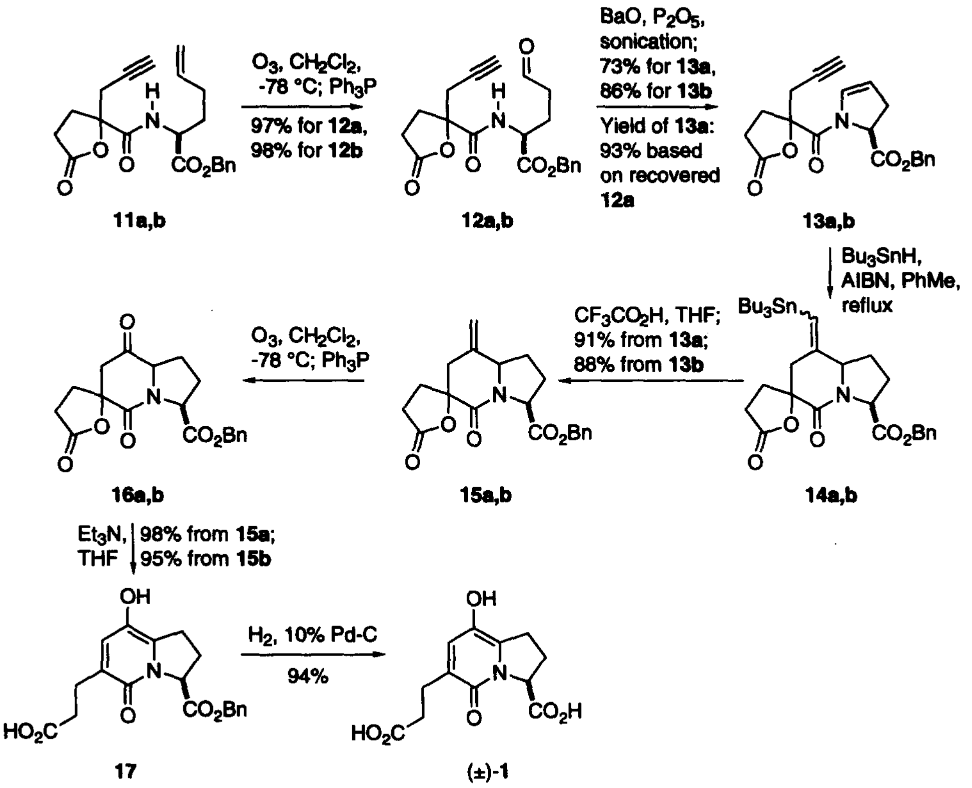


Scheme 2

94%) led to a mixture of diastereoisomers [Scheme 3, **11a** (major, 60%), and **11b** (minor, 34%)]. These were easily separated by flash chromatography, and each was then subjected to the same series of reactions.

Double bond cleavage was best effected by ozonolysis[13] (**11a** → **12a**, 97%; **11b** → **12b**, 98%), but cyclization to the enamides **13a,b** was much more difficult[14] than the corresponding reaction in the synthesis of **2**. After appreciable effort we found that sonication of a mixture of **12a** or **12b** with BaO, followed by addition of P_2O_5,[15] and continued sonication afforded the required enamides (**12a** → **13a**, 73%, or 93% corrected for recovered starting material; **12b** → **13b**, 86%, no starting material recovered).

Rapid addition (over a few sec) of a toluene solution (added in two equal portions) of Bu_3SnH (0.1 M for first portion; 0.2 M for second portion; 4.2 equiv. in all) and of AIBN (0.008 M, 0.016 M for second portion; 0.30 equiv in all) to a refluxing solution of **13a** (0.05 M) in the same solvent gave **14a** after a reflux period of *ca.* 5 h. Similarly, **13b** gave **14b**, also in high yield. Each vinyl stannane was a single compound of undetermined double bond geometry. Although the vinyl stannanes could be purified by flash chromatography, it was much more efficient to use the crude material directly for protodestannylation, which was effected by treatment with TFA. In this manner, **13a** was converted into **15a** (91% overall), and **13b** into **15b** (88%). At this point, double bond cleavage (**15a** → **16a**; **15b** → **16b**), again done by ozonolysis (O_3, CH_2Cl_2, -78 °C; Ph_3P), followed, without purification, by brief treatment with Et_3N (Et_3N, 60 °C, 1.5 h) gave the hydroxy pyridone **17** (98% from **15a**; 95% from **15b**). Finally, hydrogenolysis with H_2/ Pd-C (**17** → **1**)



Scheme 3

gave (±)-A58365A as a pale yellow, pure, crystalline solid (94% yield, mp 163-165 °C). Recrystallization from water produced clumps of very thin plates, but these did not diffract adequately for X-ray analysis.

The earlier synthesis of **2**,[2] together with the present results, establish some degree of generality for the approach of Scheme 1, and suggest that a variety of analogs should also be accessible along the same lines. It should be noted that routes in which the C(2)-C(3) double bond is introduced by conventional oxidative methods are generally marred by the sensitivity of ring B to desaturation.[3]

All new compounds, except for **16a** and **16b**, which were difficult to separate from Ph_3PO, were fully characterized by spectroscopic methods, including accurate mass measurement.

Acknowledgments

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References and footnotes

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2 Clive, D.L.J.; Zhou, Y.; de Lima, D.P. *J. Chem. Soc., Chem. Commun.* **1996**, 1463.

3 Prior syntheses of optically pure **1**: Fang, F.G; Danishefsky, S.J. *Tetrahedron Lett.* **1989**, *30*, 3621. Wong, P.L; Moeller, K.D. *J. Am. Chem. Soc.* **1993**, *115*, 11434.

4 For an example of 6-*exo* trigonal closure onto an enamide double bond, see: Yuasa, Y.; Kano, S.; Shibuya, S. *Heterocycles* **1991**, *32*, 2311.

5 Non-systematic numbering is used.

6 During the present preparation of **6**, it was found that the dimethyl ester of α-ketoglutataric acid could be most effectively made by azeotropic distillation of a solution of the acid and $TsOH.H_2O$ in MeOH-$CHCl_3$, more $CHCl_3$ being added continuously during distillation (bp *ca.* 54 °C) of the $CHCl_3$-H_2O azeotrope. Completion of the reaction is indicated by a rapid boiling point increase to *ca.* 59 °C. The $CHCl_3$ used in this experiment should be purified by the method of reference 7.

7 Calder, A.; Forrester, A.R.; Thomson, R.H. *J. Chem. Soc. (C)* **1969**, 514.

8 Although the synthesis of optically pure **7** (by the corresponding route to that shown in Scheme 2) has been reported (reference 9), considerable experimentation was needed in order to develop a reliable and efficient (>85%) method for making the organozinc (in our racemic series). A procedure for converting optically pure **8** into **10** has been described (reference 9), but we obtained far better results by using a different method for activating the zinc (Fisher Certified Zinc Metal Dust, Z-5). Activation was done under the conditions specified in reference 10, but using the proportions given in reference 11.

9 Dunn, M.J.; Jackson, R.F.W. *J. Chem. Soc., Chem. Commun.* **1992**, 319.

10 Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799.

11 Dunn, M.J.; Jackson, R.F.W.; Pietruszka, J.; Wishart, N.; Ellis, D.; Wythes, M. *Synlett* **1993**, 499.

12 EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBT = 1-hydroxybenzotriazole hydrate.

13 The Lemieux-Johnson procedure gave, in this instance, poorer yields.

14 Cyclization to 6-membered enamides appears to be easier than for the 5-membered series: *Cf.* Robl, J.A. *Tetrahedron Lett.* **1994**, *35*, 393. Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078.

15 *Cf.* Paterson I.; Cowden, C.; Watson, C. *Synlett* **1996**, 209.