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ALKYLATION OF SUCCINATES: SYNTHESIS OF RO 32-3555

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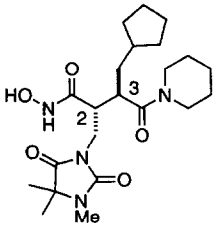
Abstract: A short synthesis, based on a succinate acylation-alkylation-decarboxylation approach, of the clinical compound Ro 32-3555 is reported. The nature of the selectivity in the mono-alkylation of succinates was examined under varying enolization conditions and in the presence of chaotropic additives.

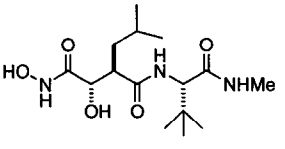
Introduction

The hydroxamic acid Ro 32-3555, or so called "Cartilage Protective Agent" (CPA) is undergoing Phase I clinical trials for rheumatoid arthritis.[1] This matrix metalloproteinase inhibitor is the third 2,3-disubstituted succinate derived hydroxamate to reach this stage of clinical development (cf. marimastat and batimastat, Figure 1). While these compounds share a common succinate backbone, their syntheses vary in length and complexity. By virtue of the C-2 hydroxyl group, the synthesis of marimastat has a unique solution starting from L-malic acid.[2] However, the dialkyl substitution present in both Ro 32-3555 and batimastat poses a greater challenge with regard to establishing the relative stereochemistry between C-2 and C-3. The solution to this problem in the synthesis of batimastat was achieved by a stereoselective Michael addition of the thiophenethiol group.[3] The Roche synthesis of Ro 32-3555 also produces a favorable ratio of the desired stereoisomer at C-2 through a decarboxylation at this carbon, but like the synthesis of the Michael acceptor for batimastat, the route to the decarboxylation precursor is lengthy.[4] Recently, Crimmin reported a more concise solution involving the selective alkylation of succinates, followed by a stereoselective epimerization.[5] This method has the advantage of rapid entry into the succinate core, using Evan's oxazolidinone chemistry[6] to establish the stereochemistry of the C-3 substituent. Herein we report a substantially shorter synthesis of Ro 32-3555 that combines the merits of both the succinate alkylation approach and the Roche decarboxylation strategy.

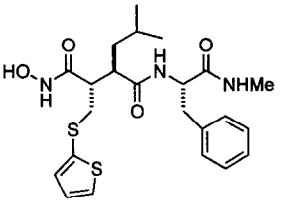
Figure 1



Ro 32-3555
(CPA)



BB-2516
(marimastat)



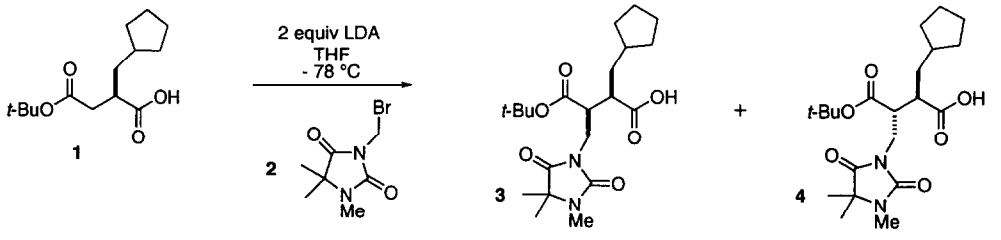
BB-94
(batimastat)

0960-894X/98/$19.00
PII: S0960-894X(97)10179-2

Chemistry and Discussion

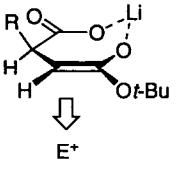
Initially, we were hopeful that the methodology described by Crimmin could be directly applied to the synthesis of Ro 32-3555. Although the alkylation of succinate **1**[7] with the bromomethyl hydantoin **2**[8] successfully provided a mixture of **3** and **4** (5–6:1; HPLC),[9] the subsequent epimerization proved to be problematic, with β-elimination of the hydantoin as the likely cause (Scheme I).

Scheme I[a]



[a](a) The following conditions all gave approximately the same ratio of **3** and **4** (5–6:1) with crude yields of 90%: enolized with LDA; enolized with LDA followed by the addition of HMPA; enolized with LDA followed by the addition of 12-crown-4; enolized with LDA in the presence of HMPA (23%).

Figure 2

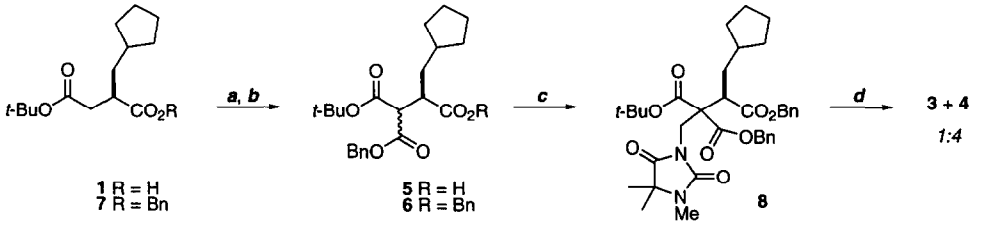


While **3** and **4** could be separated by silica gel chromatography, and the minor (desired) isomer **4** could be carried forward to Ro 32-3555, an improvement (reversal) of this ratio was sought. Attempts were made to improve the ratio by breaking up the cyclic framework (Figure 2) proposed by Crimmin[5] to explain the observed selectivity through the use of hexamethylphosphoric triamide (HMPA) and 12-crown-4. It was hoped that the addition of HMPA would have a chaotropic effect on the proposed intermediate leading to a change in selectivity. Likewise, the use of 12-crown-4 was expected to electrostatically destabilize the cyclic chelate by the sequestering of the lithium cation. Neither of these additives produced a change in the ratio of the diastereomers **3** and **4**. The ratio of **3** to **4** also proved to be insensitive to variations in enolization conditions, which when applied to more conventional esters can lead to well defined enolate geometries and product distributions.[10] Enolization with lithium diisopropylamide (LDA) in the presence of HMPA (*Z*-enolate) gave the same result as enolization in the absence of HMPA (*E*-enolate). In this regard, it is interesting to note that the conditions described by Crimmin are those employed for the generation of the *E*-enolate, which conformationally cannot form the proposed cyclic arrangement in Figure 2. These experiments suggest that the origin of the observed selectivity is not a result of a cyclic lithium chelate. Instead, it seems likely that the reaction proceeds via an acyclic intermediate wherein the selectivity is simply determined by the adjacent C-3 stereocenter. This is consistent with the observation that the stereochemical bias is always in the same sense for these succinate systems, independent of the manner in which the enol or enolate is formed, be it by enolization,[5] Michael addition,[3] or by decarboxylation.[4]

In the route described by Roche the C-2 stereocenter of Ro 32-3555 is established during a decarboxylation reaction, which yields a mixture of isomers in favor of the desired *anti* stereochemistry between C-2 and C-3.[4]

With this in mind, an effort was made to merge the two routes prior to the formation of the C-2 stereogenic center. This was accomplished by first alkylating **1** with either benzyl chloroformate[11] or benzyl cyanoformate[12] (Scheme II). The desired **5** could be separated from the residual amounts of the starting acid **1** by chromatography; however, it was more convenient to esterify the mixture and separate the esters **6** and **7**. The triester **6**, an intermediate in the Roche synthesis, was obtained in 62% overall yield from **1**. Thus, the synthesis of **6** was achieved in five steps from commercially available materials, in contrast to the twelve steps described in the Roche patent. The triester **6** was then alkylated with the bromomethyl hydantoin **2** to give **8** in 91% yield. Hydrogenolysis and decarboxylation gave a 1:4 mixture (HPLC) of **3** and **4**, respectively, which were separated by silica gel chromatography.[13]

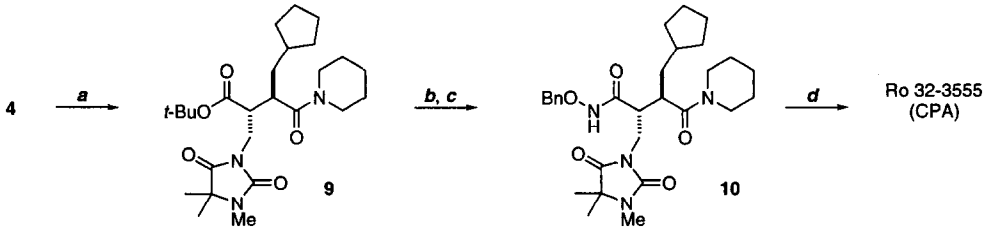
Scheme II[a]



[a](a) 2.05 equiv LDA, THF, -78 °C, then 1.05 equiv of either benzyl chloroformate or benzyl cyanoformate (added rapidly), 3 h. (b) Cs_2CO_3, benzyl bromide, DMF, 22 °C, 24 h, **6** was obtained in 62% from **1**. (c) NaH, DME, **2**, 22 °C, 20 h, 91%. (d) H_2 45 psi, 10% Pd on C, *i*-PrOH, 23 °C, 2 h, then Et_3N, PhMe, reflux, 2 h, **3** + **4** 71%.

From the desired major isomer **4**, the synthesis of Ro 32-3555 was completed in a manner analogous to the reported synthesis[4] as shown in Scheme III. BOP[14] mediated coupling with piperidine gave **9** in 92% yield. Deprotection of the *tert*-butyl ester and coupling with *O*-benzylhydroxylamine gave **10**, which upon careful hydrogenolysis[15] of the benzyl ether yielded Ro 32-3555.[16]

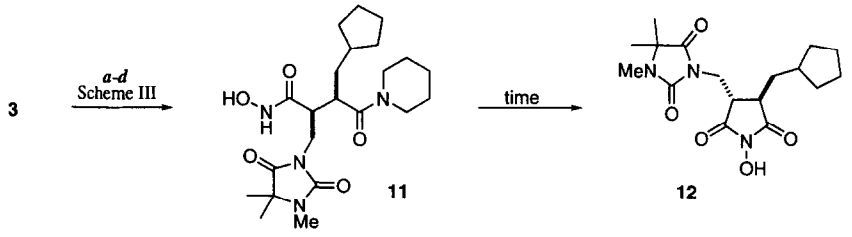
Scheme III[a]



[a] (a) BOP, Et_3N, piperidine, CH_2Cl_2, 0–22 °C, 15 h, 92%. (b) trifluoroacetic acid, 22 °C, 5 h, 100%. (c) BOP, Et_3N, $BnONH_2$·HCl, CH_2Cl_2, 0–22 °C, 8 h, 77%. (d) H_2 30 psi, 5% Pd on $BaSO_4$, MeOH, 1 h, 23 °C, 100%.

Interestingly, **11** derived from the isomeric **3** through the same sequence of reactions cyclized upon standing as a solution in methanol to give the *N*-hydroxysuccinimide **12** (Scheme IV). In contrast, Ro 32-3555 shows no such tendency, no doubt as a reflection of the energetic difference between the *cis* and *trans* *N*-hydroxysuccinimide products.[17]

Scheme IV



Conclusion

A concise synthesis of Ro 32-3555 was achieved by a succinate acylation-alkylation-decarboxylation strategy. This composite of the Roche and Crimmin methods owes its brevity to the significantly fewer number of steps required to prepare the Roche triester **6**. Although the synthesis is specific for Ro 32-3555, it potentially represents a general solution to the construction of 2,3-disubstituted succinates that contain groups pendant from C-2 that are susceptible to β-elimination.

Acknowledgment

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Footnotes and References

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7. Prepared as described in ref 5 starting with (*S*)-(-)-4-benzyl-2-oxazolidinone and 3-cyclopentylpropionyl chloride.
8. Prepared in two steps from the known (Schläpfer-Dähler, M.; Mukherjee-Müller, G.; Heimgartner, H. *Helv. Chim. Acta* **1992**, *75*, 1251) 1,5,5-trimethylimidazolidine-2,4-dione: 1) aqueous 37% formaldehyde, reflux, 18 h; 2) PBr_3, Et_2O, 23 °C.
9. The stereochemistry of **3** and **4** is based on the work in ref 5.
10. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) For a discussion of ester enolate equilibria see: Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451.
11. For a related example see: Brocksom, T. J.; Petragnani, N.; Rodrigues, R. *J. Org. Chem.* **1974**, 39, 2114.
12. For a related reaction see: Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
13. 35:64:1 hexanes:EtOAc:HOAc.
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16. This material was spectroscopically consistent with the reported material (see ref 4).
17. The difference in energy is estimated at ca. 2 kcal based on 6-31G* ab initio calculations (Gaussian94™) of the *cis* and *trans* isomers of 1-hydroxy-3,4-dimethylpyrrolidine-2,5-dione.