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Diastereoselective Synthesis of 2,3,6-Trisubstituted Tetrahydropyran-4-ones via Prins Cyclizations of Enecarbamates: A Formal Synthesis of (+)-Ratjadone A

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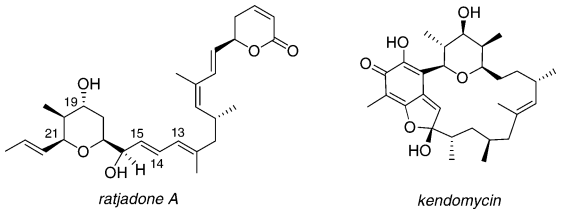
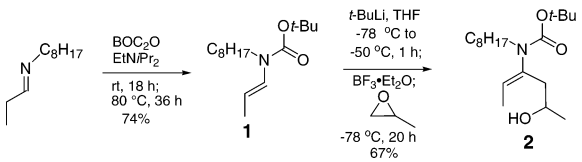
Tetrahydropyrans of varied substitution patterns are embodied in the structures of numerous natural products. Ratjadone A and kendomycin are two representative examples that possess more densely substituted tetrahydropyrans and have in common a frequently observed 2,3,6-all-*cis* stereochemical pattern.[1] Accordingly, many strategies for the construction of these substructures have been developed, and by far the most direct approach involves the cyclization of alkenes with oxocarbenium ions, the Prins cyclization.[2] Despite the fact that a considerable amount of effort



has been directed toward improving the efficiency of the Prins cyclization, primarily by increasing the nucleophilicity of the alkene reactant,[3] this method has not been extensively applied in natural product syntheses. Indeed, the majority of the synthetic effort has been directed toward natural products containing the less complex 2,6-disubstituted tetrahydropyran substructures,[4] perhaps due to the inaccessibility of nonracemic Prins cyclization precursors and/or inferior cyclization diastereoselectivities for the more complex substitution patterns.[5] We report herein that enecarbamates participate in highly diastereoselective Prins cyclizations with oxocarbenium ions en route to all-*cis*-2,3,6-trisubstituted tetrahydropyran-4-ones and, moreover, show that the cyclization substrates can be quickly assembled from readily available optically pure epoxides in the context of a formal total synthesis of (+)-ratjadone A.

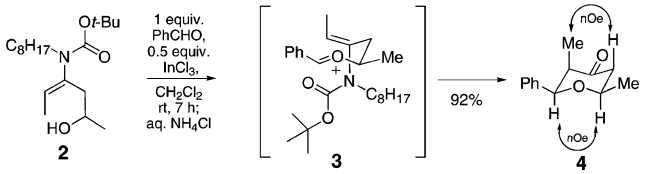
The preparation of the enecarbamates such as **2** required for the Prins cyclization study (Scheme 1) was easily accomplished in a two-pot reaction sequence. Thus, the enecarbamate **1** was prepared via acylation of the *N*-octyl imine derivative of propanal by modification of a protocol previously reported by Bach.[6] Treatment of enecarbamate **1** with *t*-BuLi[7] followed by the addition of propylene oxide and $BF_3{\cdot}OEt_2$ gave the desired reactant for the Prins cyclization, homoallylic alcohol **2** (single regioisomer, 67% yield). Similar products were obtained by substitution of the propylene oxide with styrene oxide, cyclohexene oxide, or ethylene oxide to furnish the alcohols shown in entries 2 (77%), 5 (53%), and 6 (53%) of Table 1, respectively.

Scheme 1



We initially subjected the alcohol **2** to the mild Lewis acid conditions reported by Dobbs[3b] for Prins cyclizations of homoallylic alcohols with aldehydes, namely, $InCl_3$ in methylene chloride (Scheme 2). We were pleased to discover that alcohol **2** and benzaldehyde provided the all-*cis* tetrahydropyran-4-one **4** in excellent yield accompanied by comparable amounts of *N*-BOC-octylamine. Presumably, this transformation proceeds by cyclization of the diequatorial, chairlike conformer of the oxocarbenium ion **3** to provide an *N*-acyliminium ion that is then hydrolyzed by the equivalent of water produced from the formation of the oxocarbenium ion.

Scheme 2



Additional Lewis acids were also examined and found to afford the same product but in diminished yields and accompanied by trace amounts of another diastereomer: $BF_3{\cdot}OEt_2$ (−78 to 0 °C, 83%); $Bi(OTf)_3$ (−78 °C, 82%); TMSOTf with TMS ether of **2** (−78 to −20 °C, 71%).

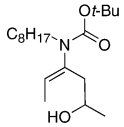
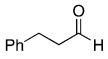
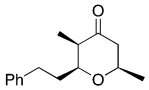
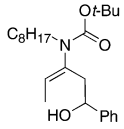
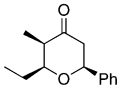
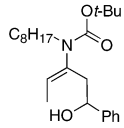
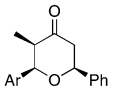
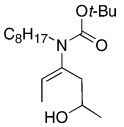
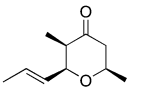
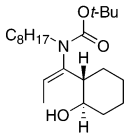
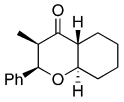
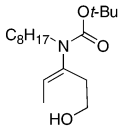
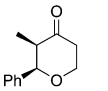
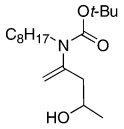
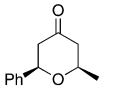
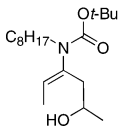
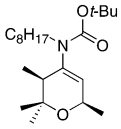
The scope and generality of this variant of the Prins cyclization is presented in Table 1. The preferred Lewis acid, $InCl_3$ (0.5 equiv), was employed in all of the examples except for entry 7. Entries 1 and 2 demonstrate that saturated aldehydes also participate in this reaction. Cyclization with an unsaturated aldehyde (entry 4) is also uneventful and relevant to the ratjadone A application, vide infra. Substitution patterns other than the 2,3,6-trisubstituted examples are also accessible, e.g., 2,3,5,6-tetrasubstituted (entry 5), 2,3-disubstituted (entry 6), and 2,6-disubstituted (entry 7). Finally, a ketone is also a suitable reaction partner but, in this case, affords an enecarbamate product in modest yield (entry 8).

We next directed our attention toward the synthesis of ratjadone A, which has been shown to exhibit cytotoxicities in the picomolar range on several established cell lines (L929, KB-3.1, KB-V1, K-562, PC-3)[1b,c] and functions by inhibiting nuclear export by blocking CRM1/exportin 1.[1c] Total syntheses of (+)-ratjadone A and its enantiomer have been reported by the Kalesse[8a,b] and Williams[8c] groups, respectively.

In both syntheses, the challenging 2,3,6-trisubstituted tetrahydropyran substructure was prepared by initial introduction of the C(19−21) stereogenic centers followed by 6-*exo*-ring closure of an epoxy alcohol. Thus, Kalesse prepared the tetrahydropyran **9** (Scheme 3) in 14 steps from (*R*)-4-benzyl-2-oxazolidinone, which was then converted to (+)-ratjadone A in 5 steps via a Heck reaction with a C(13) vinyl iodide segment. In view of this efficient endgame, the preparation of tetrahydropyran **9** by the Prins cyclization of the appropriate enecarbamate became our objective.

10.1021/ja046940r CCC: $27.50

Table 1. Prins Cyclizations of Enecarbamates

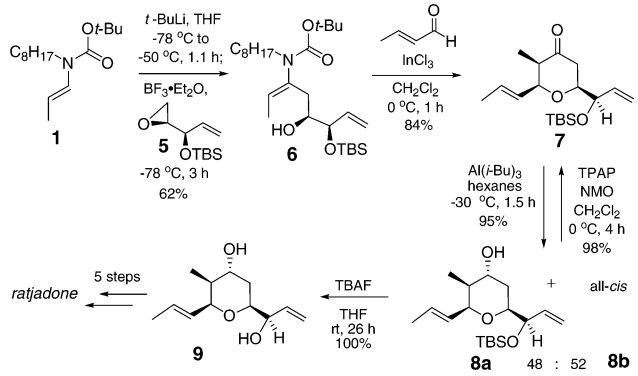
entry	enamide	aldehyde (2 equiv.) temperature, time	product[a]	yield
1		 rt, 5 h		80%
2		 0 °C to rt, 13 h		70%
3		 0 °C to rt, 2.5 h Ar = *p*-tolyl		74%
4		 0 °C to rt, 4.5 h		91%
5		 rt, 2 h		84%
6		 0 °C to rt, 5 h		83%
7		 1. TMSCl, rt, 21 h 2. TMSOTf, CH_3CN -78°C, 40 min		60%
8		 (10 equiv.) rt, 24 h		49%

[a] >95:5 by ^{1}H NMR analysis of crude reaction mixture. See Supporting Information for stereochemical assignments based upon diagnostic NOEs.

To that end, the known optically pure epoxide **5** was prepared by a Sharpless asymmetric epoxidation of divinylcarbinol[9] followed by silylation and then subjected to the vinyl anion derivative of enecarbamate **1** to afford the key homoallylic alcohol **6**. Treatment of enecarbamate **6** with crotonaldehyde in the presence of $InCl_3$ furnished the tetrahydropyranone **7** as a single diastereomer in good yield (84%). Reduction of pyranone **7** with sodium borohydride gave exclusively the undesired all-*cis* alcohol **8b** whose Mitsunobu inversion was problematic due to competing elimination. Accordingly, a variety of ketone reducing agents were surveyed, and it was found that triisobutylaluminum hydride produced a nearly equal amount of stereoisomeric alcohols **8a** and **8b**. The undesired alcohol **8b** could be readily recycled by oxidation to pyranone **7**. The desired alcohol **8a** was deprotected to afford diol **9** whose spectral properties were identical with those reported by Kalesse,[8a] which thereby constitutes a formal total synthesis of (+)-ratjadone A.

In conclusion, we have shown that enecarbamates are excellent terminating groups for Prins cyclizations. A noteworthy feature of this methodology is the easy, stereoselective construction of the cyclization precursors by alkylation of metalated (*E*)-enecarbamates with epoxides. The stereochemistry of the resultant trisubstituted

Scheme 3



(*E*)-enecarbamates is then transferred with high fidelity to afford the frequently observed and biologically significant all-*cis*-2,3,6-trisubstituted tetrahydropyran substructures of naturally occurring compounds. This methodology facilitated an exceptionally concise formal total synthesis of the nuclear export inhibitor (+)-ratjadone A, and its further development and application is underway.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ratjadone A: (a) Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1995**, 685. (b) Gerth, K.; Schummer, D.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1995**, 973. Ratjadones B−D: (c) Köster, M.; Lykke-Anderson, S.; Elnakady, Y. A.; Gerth, K.; Washausen, P.; Höfle, G.; Sasse, F.; Kjems, J.; Hauser, H. *Exp. Cell Res.* **2003**, 321. Kendomycin: (d) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 323. FR901464: (e) Nakajima, H.; Sato, B.; Fujita, T.; Takase, S.; Terano, H.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 1196. Phorboxazoles A, B: (f) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. Sorangicin A: (g) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Höfle, H. *Tetrahedron Lett.* **1985**, *26*, 6031. Lasonolide A: (h) Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015.

(2) For a recent review of Prins cyclizations, see: Snider, B. B. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 2, p 527.

(3) For selected recent examples of vinyl silanes, see: (a) Viswanathan, G. S.; Yang, J.; Li, C. J. *Org. Lett.* **1999**, *1*, 993. (b) Dobbs, A. P.; Martinovic, S. *Tetrahedron Lett.* **2002**, *43*, 7055. Allyl silanes, see: (c) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955. (d) Leroy, B.; Markó, I. E. *J. Org. Chem.* **2002**, *67*, 8744. (e) Yu, C. M.; Lee, J. Y.; So, B.; Hong, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 161. (f) Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189.

(4) Completed natural products syntheses include the following. Apicularen: (a) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. Catechols 1 and 2: (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407. Leucascandrolide: (c) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420.

(5) Preparation of the 2,3,5,6-tetrasubstituted tetrahydropyran subunit by a Petasis−Ferrier rearrangement in a total synthesis of phorboxazole is an exception; see: (a) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. For other examples of Prins cyclizations leading to all-*cis*-2,3,6-trisubstituted tetrahydropyrans, see: (b) Patterson, B.; Rychnovsky, S. D. *Synlett* **2004**, 543. (c) Barry, C. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (d) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499. (e) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (f) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (g) Markó, I. E.; Chelle, F. *Tetrahedron Lett.* **1996**, *38*, 2895. In addition, several of the tetrahydropyrans enumerated in ref 3d above are all-*cis*-2,3,6-trisubstituted but possess a C(3) oxygen rather than a carbon substituent.

(6) Bach, T.; Schröder, J. *J. Org. Chem.* **1999**, *64*, 1265.

(7) (a) Whisler, M. C.; Soli, E. D.; Beak, P. *Tetrahedron Lett.* **2000**, *41*, 9527. (b) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *53*, 4437.

(8) (a) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885. (b) Kalesse, M.; Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Saeed, A.; Buzlaff, A.; Kasper, C.; Haustedt, L. O.; Hofer, E.; Scheper, T.; Beil, W. *ChemBiochem* **2001**, *2*, 709. (c) Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383.

(9) Romero, A.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 8264.

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