J|A|C|S
COMMUNICATIONS

Published on Web 02/02/2006

Comparative Diels−Alder Reactivities within a Family of Valence Bond Isomers: A Biomimetic Total Synthesis of (±)-UCS1025A

Thomas R. Hoye* and Vadims Dvornikovs

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received December 2, 2005; E-mail: hoye@chem.umn.edu

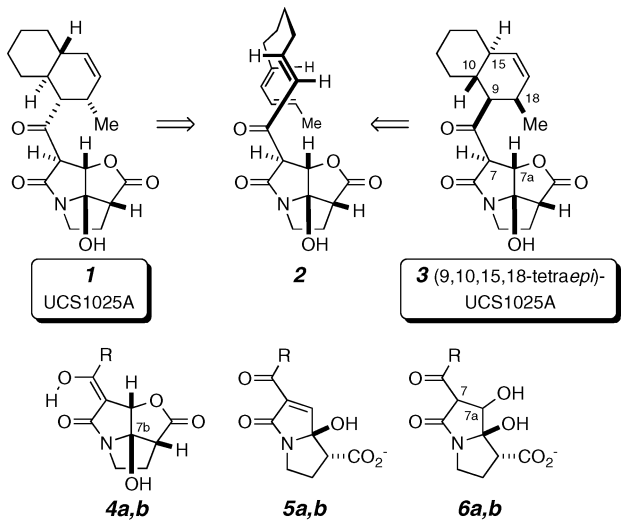
UCS1025A (**1**) was isolated from fermentation broth of a fungus (*Acremonium* sp.)[1] and its structure subsequently reported in 2002.[2] The first total synthesis of this structurally fascinating heteratriquinane was recently achieved.[3] This natural product has antimicrobial,[1] cytotoxicity,[1] and telomerase inhibition[2,3] properties. From the outset of our synthesis studies, we were motivated, among other things, by the question of how octalin formation occurs during the biosynthesis of **1**. It seems likely that an intramolecular Diels−Alder (IMDA) cycloaddition within a triene such as **2** is operative.[4] We are intrigued by whether that event requires enzymatic catalysis[5] or, instead, might be sufficiently fast to account for formation of **1** spontaneously, under biologically relevant conditions. Answers to the following questions would form a basis for considering this issue, not only for UCS1025A (**1**) but also for many other members of the larger class of octalinoyl tetramic acid-like natural products. Would the nonenzymatic reaction be fast enough to be the natural event? If so, would the chiral heterocyclic moiety in **2** induce significant diastereocontrol?

These questions become both more challenging to address and more fascinating to consider in light of the facile interconversions among isomeric species **1**, **4a** (the enol), and **5a** (the ring-opened carboxylate) that were observed during the original isolation studies of UCS1025A.[2] In the aprotic organic solvent $CDCl_3$, keto tautomer **1** predominates. The enol form **4a** selectively crystallized from *n*-hexane/acetone, then slowly reverted back to **1** upon redissolution in $CDCl_3$. When added to a pH 7.2 phosphate buffer in D_2O, **1** ring opened to the carboxylate **5a**. A small portion of this electrophilic enedione then spontaneously hydrated to provide the diol **6a**. It is fully reasonable to think that the substrate triene **2** would also access the analogous isomeric species **4b**−**6b**. This further adds to the intrigue of the Diels−Alder event since each of these discrete species possesses dienophilic character—the reaction rate and diastereoselectivity would be unique to each of these structures.

The concise construction of the vinyl iodide **12**, a precursor to the manifold of diene intermediates **2**/**4b**/**5b**, is shown in Scheme 2. We began by developing[6] an intramolecular Mukaiyama-like addition reaction in which the α-carbon of a side chain butyrate ester adds (via its ketene acetal, generated in situ) to one of the imide carbonyl groups (presumably activated by in situ silylation) in substrate[7] **7**. Methyl ester **8** is formed with a very high level of diastereocontrol (dr > 30:1). Acid **9** can be isolated and handled, but over time, it cyclized to tricyclic lactone **10**—an event we regarded both as evidence for the *endo* orientation of the carboxylate and as a good harbinger. Acid **9** smoothly underwent sequential iodolactonization to **11** and silylative ring opening to the TIPS-ether/TIPS-ester derivative **12**.

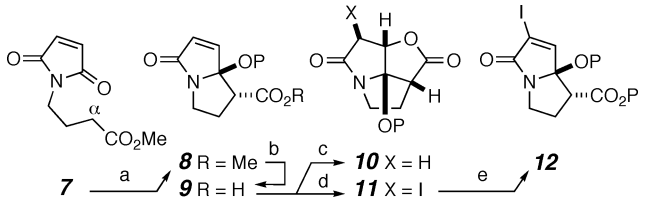
Magnesium−iodine exchange between **12** and *i*-PrMgCl followed by acylation with the Weinreb amide **13**[8] gave **14**, the bis-TIPS analogue of **5b** (Scheme 3). This substrate underwent cycloaddition with a $t_{1/2}$ of ca. 6 days at room temperature and 3 h at 65 °C in $CDCl_3$ to provide, predominantly,[9] a ca. 4:3 ratio of two isomeric adducts, which were not amenable to separation by either normal

Scheme 1



a R = methyloctalinyl (as in ***1***) ***b*** R = undeca-1,7,9-trienyl (as in ***2***)

Scheme 2 [a]



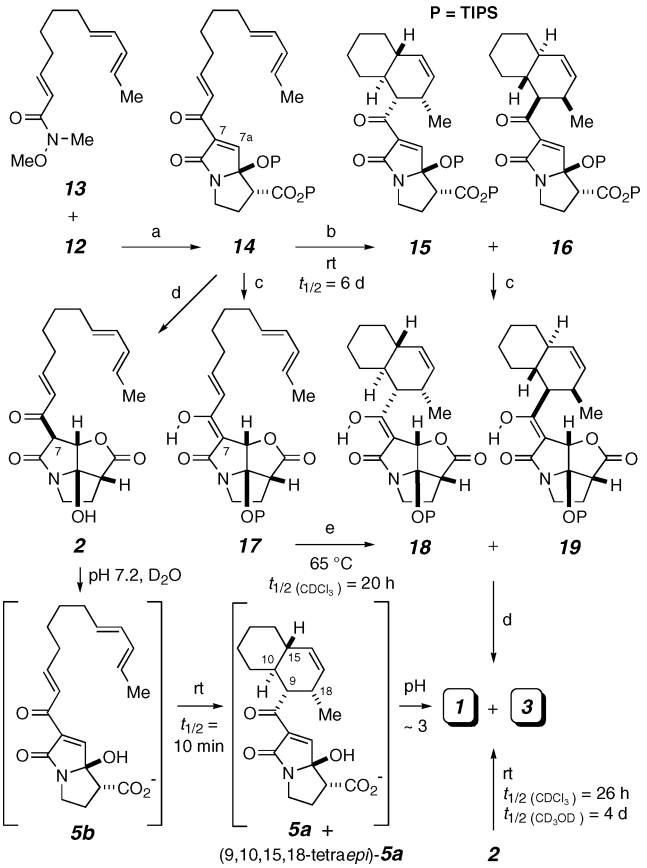
[a] Throughout: P = TIPS (*i*-Pr_3Si). (a) TIPSOTf, Et_3N, $CHCl_3$, rt, 97%; (b) LiOH, THF, H_2O, rt, 97%; (c) C_6D_6, 80 °C, quantitative (by ^1H NMR); (d) $NaHCO_3$, H_2O, CH_2Cl_2; I_2, rt, 93%; (e) TIPSCl, Et_3N, Et_2O, rt, 82%.

or reversed-phase chromatography. By virtue of eventual transformation of this mixture into UCS1025A (**1**) and its tetraepimer **3**, these were proven to be compounds **15** and **16**. Both result from an *endo* mode of addition.[9] This sense of diastereoselectivity, as well as the rate of cyclization, is to be contrasted with the thermal IMDA of the amide **13** itself, which required 5−6 days at 165 °C and proceeded with 1:3 *endo:exo* selectivity.[8] Thus, the substrate control expressed in the IMDA of **14** favors *endo* addition, but facial selectivity for approach of the diene to the C9−C10 dienophile is virtually nonexistent—perhaps a reflection of the remote nature of the stereocenters in **14**.

The TIPS ester in **15**/**16** was selectively removed (KF, MeOH) to give **18**/**19**. Within the limits of detection by ^1H NMR analysis, each of these mono-TIPS ether derivatives existed exclusively as an enol (and they are, like **15**/**16**, inseparable in our hands). This tautomeric preference suggests that the hydroxyl group of the free carbinolamide in **1** (and **3**) is important in stabilizing the keto form by way of an internal hydrogen bond, which is absent in **18**/**19**. More forcing desilylation conditions (excess HF•py) cleaved the tertiary silyl ether group in **18**/**19** or, equally well, both TIPS groups

10.1021/ja0581999 CCC: $33.50

Scheme 3 [a]



[a] Throughout: P = TIPS (*i*-Pr_3Si). (a) *i*-PrMgCl, THF/ether, −50 °C, 10 min; then **13**, −50 °C to rt, 35%; (b) $CDCl_3$, 65 °C, 2 days, 69%; (c) KF, MeOH, rt, 5 min, 70−100%; (d) HF•py, MeCN, rt, 2 days (56% to **1** + **3** from **17**; 74% to **2**); (e) $ZnCl_2$•Et_2O, CH_2Cl_2, rt, ca. 18 h, 56% or $CDCl_3$, 65 °C.

in **15**/**16** to produce UCS1025A (**1**) and tetra-*epi*-UCS1025A (**3**).[10] The structure of the unnatural isomer **3** rests primarily on thorough analysis of its ^{1}H NMR spectrum, which established that **3** possesses the same relative configuration as **1** within each of the (spectroscopically isolated) octalin and heterocyclic moieties.

We returned to the bis-TIPS tetraene **14** and selectively cleaved the ester (KF, MeOH) to provide a new Diels−Alder substrate, the tricyclic lactone **17** (the TIPS-protected analogue of **2**). As with **18**/**19**, this silyl ether was seen only as its enol tautomer, which is consistent with the role of the internal hydrogen bond hypothesized above. No cyclization of **17** was observed over several days at ambient temperature (rt), and even at 65 °C in $CDCl_3$, the $t_{1/2}$ for formation of **18** and **19** (dr 1:2) was ca. 20 h.

Both TIPS groups were removed in **14** (excess HF•py) to provide our putative, natural Diels−Alder substrate **2**. This compound appeared exclusively as the keto tautomer in $CDCl_3$ but with a slight preponderance for the enol **4a** in CD_3OD. It underwent very clean [4 + 2] cycloaddition at room temperature with a $t_{1/2}$ of ca. 26 h in $CDCl_3$ and 4 days in CD_3OD. The ratio of the natural:unnatural isomers, **1**:**3**, was ca. 1:3.

Finally, and most intriguing of all, when **2** was dissolved in phosphate buffer (pH 7.2, D_2O, 100 mM), it immediately ring opened to **5b** (^{1}H NMR), which rapidly cyclized to a nearly 1:1 mixture[10] of **5a**:**(tetraepi)-5a**[11] with a $t_{1/2}$ of 10 min! The extent to which this rate acceleration for cyclization of **5b** is due to the aqueous medium[12] alone versus the difference in electronic character of its dienophilic moiety is under study. Regardless, this remarkably fast IMDA reaction under biologically relevant conditions establishes a temporal boundary condition within which enzyme catalysis would need to function, if it is operative in the biosynthesis of **1**.

To summarize, a biomimetic total synthesis of (±)-USC1025A (**1**) involving seven linear steps from known **7** was achieved. IMDA reactions of an array of substrates, varying in structure of the dienophilic subunit, are compared. The rate of cycloaddition of carboxylate **5b** is sufficiently fast to be easily compatible with the hypothesis that **1** is formed in vivo by a nonenzyme catalyzed event. On the other hand, the lack of a substantial level of diastereoselectivity observed to date for this substrate-controlled IMDA reaction would suggest otherwise. Experiments directed toward identification of biologically relevant yet nonenzymatic conditions (e.g., aqueous, metal-ion mediated) resulting in more highly stereoselective formation of **1** are ongoing.

Acknowledgment. This investigation was supported by a grant awarded by the DHHS (GM-65597). We thank Professor S. J. Danishefsky for generously providing a pre-publication version of ref 3.

Supporting Information Available: Spectroscopic characterization data and experimental procedures for compounds **1**−**3**, **8**−**12**, and **14**−**19** (16 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Nakai, R.; Ogawa, H.; Asai, A.; Ando, K.; Agatsuma, T.; Matsumiya, S.; Akinaga, S.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 294−296. (b) Akama, T.; Asai, A.; Nara, S.; Yamashita, Y.; Agatsuma, T.; Mizukami, T.; Ikeda, S.; Saitoh, Y. WO 01/29043, 2001.

(2) Agatsuma, T.; Akama, T.; Nara, S.; Matsumiya, S.; Nakai, R.; Ogawa, H.; Otaki, S.; Ikeda, S.; Saitoh, Y.; Kanda, Y. *Org. Lett.* **2002**, *4*, 4387−4390.

(3) Lambert, T. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 426−427. In the strategy used in this work, preformed heterocyclic and octalin subunits were joined using an elegant, late stage, C7−C8 bond formation.

(4) For use of an IMDA in the synthesis of the tetramic acid/octalin containing natural product, equisetin, see: Burke, L. T.; Dixon, D. J.; Ley, S. V.; Rodríguez, F. *Org. Biomol. Chem.* **2005**, *3*, 274−280.

(5) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321−352.

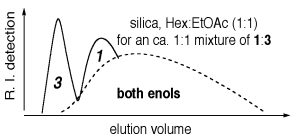
(6) Dvornikovs, V.; Hoye, T. R. *Abstr. Pap.—Am. Chem. Soc.* **2005**, *229*, 665-ORGN. Details of this mild enolization/aldolization process will be reported elsewhere. Maleimide **7** was quickly and nonproductively consumed when treated with either of the strong bases LDA or *t*-BuOK.

(7) Stuhlmann, F.; Jäschke, A. *J. Am. Chem. Soc.* **2002**, *124*, 3238−3244.

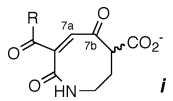
(8) Lygo, B.; Bhatia, M.; Cooke, J. W. B.; Hirst, D. J. *Tetrahedron Lett.* **2003**, *44*, 2529−2532.

(9) A pair (again ca. 4:3) of minor isomers (<10% of the major pair), which we surmise to be the two *cis*-fused *exo*-adducts, was detected (^{1}H NMR).

(10) Facile keto−enol tautomerization conspired to make separation of the natural and unnatural isomers **1** and **3** frustratingly challenging. These difficulties, first revealed by 2D TLC studies, are evident in the following, typical chromatogram. Multiple recyclings eventually gave a sample of **1** sufficiently enriched that purity could be upgraded by crystallization as its enol **4a**, which then retautomerized to **1** in $CDCl_3$ at room temperature (final equilibrium ratio of **1**:**4a** = ca. 11:1).



(11) Notably, **1** or **3** opens in buffer to **5a** or **tetraepi-5a**, yet neither equilibrates to a mixture of the two. This rules out a facile, deep-seated tetraepimerization of all stereocenters within the bisheteratriquinane that can be envisioned to occur via the monocyclic, ζ-lactam **i**.



(12) (a) Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816−7817. (b) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897−1900. (c) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365−1372.

JA0581999