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Tetrahedron Letters 45 (2004) 3827–3829
Tetrahedron Letters

Probing competitive pathways in building a hydroazulene moiety by reductive cyclization

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Received 18 December 2003; accepted 16 February 2004

Abstract—Deuterium tracing and deuterium isotope effects demonstrate competitive pathways for the reduction of vinyl iodide in **3** (in the context of a proximal keto function) en route to guanacastepene.
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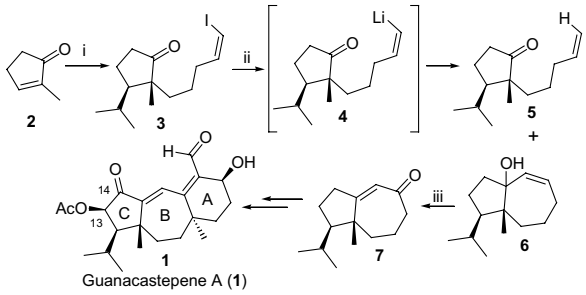
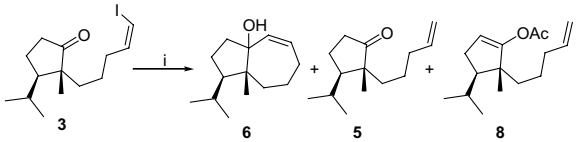
Recently, we described the total synthesis[1] of the structurally novel diterpenoid guanacastepene[2,3] (**1**). Among the issues that had to be addressed was that of building the hydroazulene (BC) sector. We hoped to solve the total synthesis problem via the intermediacy of a hydroazulene (**7**) with the expectation that the functionality at carbons 13 and 14 could be installed in the closing phases of the venture. As matters progressed, **7** was obtained by oxidative rearrangement of **6**.[1a,4] We hoped to reach compound **6** by reductive cyclization of **3**,[5,6] presumably via its vinyllithium equivalent **4**.[7] Compound **3** was to be reached by a stereocontrolled *trans* β,α-dialkylation sequence, starting with α-methylcyclopentenone.

The general outline of Scheme 1 was realized.[1] Indeed, this program lent itself to scale-up to the point where it serviced the total synthesis of **1** (which turned out to be somewhat complex in its late stages). A weak aspect in the translation of Scheme 1 to practice arose in the reductive cyclization step. In practice, the reaction leading from **3** → **6** was always accompanied by substantial formation of **5**, in which reduction had not led to cyclization. Ultimately, a set of conditions was devised to provide a 2.5:1 ratio of **6**/**5** on large scales, which allowed the synthesis to progress.

Since reductive cyclization of ω-halocarbonyl compounds is an important reaction type in organic synthesis,[8] we undertook to explore the features that influence the ratio of **6**/**5** arising from the reduction of **3**. The first important observation was that increased dilution favored reductive cyclization (cf. **6**) relative to reduction (cf. **5**). However, the practicalities associated with scaling up this reaction limited the extent to which high dilution could be exploited, while still bringing forward significant sums of material.



Scheme 1. (i) (a) Ref. 9, 94%, (b) MeLi, THF, 0 °C, 1 h, then 2.5 equiv of 5-iodo-1-pentene, HMPA, −78 °C to rt, 63–72%, (ii) 5.0 equiv *n*-BuLi (inverse addition), 0 °C, THF, 30 min, (iii) PCC, MS 4 Å, CH_2Cl_2, 70–92%.



Scheme 2. (i) 5.0 equiv *n*-BuLi inverse addition, 0 °C, THF, 30 min, then Ac_2O.

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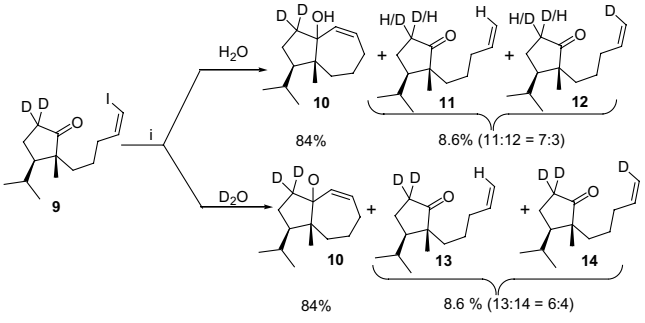
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.02.161

Another revealing finding was, that quenching of the pre-workup reaction mixture, from the reaction of **3** with *n*-BuLi with acetic anhydride resulted in the formation of significant amounts (ca. 16%) of **8** (Scheme 2).[1a] Thus, enolate formation accounted for at least half of the noncyclizing reductive pathway. These results suggested that exchange between vinyllithium intermediate **4**,[7] and one or both of the protons, to the ketone of **3** were involved in favoring reduction at the expense of reductive cyclization. The impact of dilution in favoring reductive cyclization in substrate **3**, suggested that there was a significant intermolecular component in the premature quenching of vinyllithium reagent (**4**).

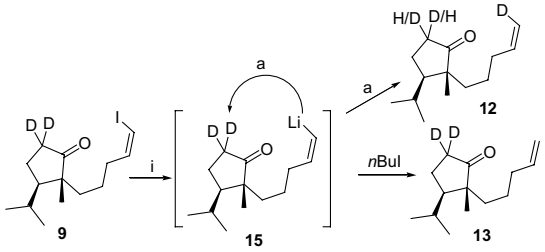
We then examined the consequences of deuteration α to the ketone in **3**, on the reductive cyclization:reduction ratio. Indeed, when the reaction was conducted on the bis deutero compound **9**, the ratio of cyclization product versus noncyclizing reduction products was substantially improved from the usual optimal 2.5:1 to ca. 10:1.[1c]

It was of interest to study the residual noncyclized reduction product, discerned in the case of dideutero substrate **9**.[10] Interestingly, under standard metal–halogen exchange conditions, upon quenching with H_2O, only 30% of the total uncyclized product was deuterated at the vinylic position (cf. **12**). Examination of the ^1H NMR spectrum of the reduction product mixture of **11** and **12** shows that, the deuterium had been introduced at the vinyl group with retention of configuration. We emphasize that given the configurational stability of such vinyllithium species,[11] the experiment described above does not teach whether the vinyllithium → lithioenolate exchange is intra- or intermolecular (Scheme 3).

We next focused on the ratio of vinylic deuterated reduced product **11** and its nondeuterated congener **12**, obtained in this process. Quenching the reaction mixture with D_2O, had only a minor effect on the increment of deuterium incorporation on the vinylic position (now the formation of **14** is ca. 40% of the total uncyclized product) (Scheme 3). Clearly there is very little potentially 'active' vinyllithium specie prior to work-up. It was further found that conducting the reaction in perdeutero tetrahydrofuran, had no consequences on incorporation of deuterium in the vinylic position of the product. Accordingly, we tend to the surmise that the



Scheme 3. (i) 5.0 equiv *n*-BuLi (inverse addition), 0 °C, THF, 30 min.



Scheme 4. (i) 5.0 equiv. *n*-BuLi (inverse addition), 0 °C, THF, 30 min.

premature quenching of the vinyllithium intermediate **15**, arises from the *n*-butyl group, presumably via an E2 like elimination of 1-iodobutane,[12] formed as a consequence of the initial metal–halogen exchange reaction of **9** (Scheme 4).

In summary then, the predominant source of nonring forming reduction, in the nondeuterated series (cf. **3**), is vinyllithium–lithioenolate exchange. As we proceed to the dideutero substrate **9**, this pathway is suppressed and the ratio of reductive cyclization is sharply improved at the expense of nonring forming reduction. Furthermore, in the case of **9**,[13] E2 elimination becomes somewhat more prominent as a minor 'pre-workup' quenching pathway, relative to vinyllithium–lithioenolate exchange (i.e. the ratio of **11/12** starting with **9**, is ca. 7:3).

As pointed out earlier, in the end, the synthesis was accomplished despite the difficulties arising from competitive formation of **5** and **6** from substrate **3**. Nonetheless the studies described above serve to underscore the sorts of problems that may beset reductive cyclization reaction, and the manner in which these problems can be evaluated in a qualitative fashion, at least.

Acknowledgements

The research was supported by the National Institutes of Health (HL25848 and CA28824). We thank Dr. Gregory B. Dudley for helpful discussions. Anna Dudkina (NMR Core Facility, Sloan-Kettering Institute, CA 02848) is acknowledged for mass spectral analysis.

References and notes

1. Total synthesis: (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399–2402; (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789–6791; (c) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605–5606; (d) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188–2191; (e) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185–2188; (f) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030–1042.

2. For recent synthetic studies inspired by guanacastepene cf. inter alia: (a) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491–3494; (b) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469–7472; (c) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923–1926; (d) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947–4950; (e) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605–9609; (f) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975–6978; (g) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063–1066; (h) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233–4237; (i) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363–3366; (j) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959–3962; (k) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033–4036; (l) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063–2066; (m) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123–9126; (n) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569–572; (o) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113–4115.
3. Isolation: (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2117; (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901; (c) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256–261.
4. (a) Büchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021–2023; (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.
5. Corey, E. J.; Kuwajima, I. *J. Am. Chem. Soc.* **1970**, *92*, 395–396.
6. Piers, E.; Walker, S. D.; Armbrust, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 633–637.
7. Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839–4842; In our analysis we deliberately avoided dealing with the interesting question as to whether cyclization involves a mature vinyllithium species, or radical anionoid species en route to the fully formed vinyllithium entity, cf. inter alia: Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023–9042.
8. An early example of the use of reductive cyclization occurs in the context of our total synthesis of patchouli and *epi*-patchouli alcohol: Danishefsky, S. J.; Dumas, D. *Chem. Commun.* **1968**, 1287–1288; For more recent work in this area cf. inter alia: (a) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590–602; (b) Piers, E.; Cook, K. L.; Rogers, C. *Tetrahedron Lett.* **1994**, *35*, 8573–8576; (c) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972–2976; (d) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11–13; (e) Mori, M.; Kaneta, N.; Isono, N.; Shibasaki, M. *Tetrahedron Lett.* **1991**, *32*, 6139–6142; (f) Mori, M.; Watanabe, N.; Kaneta, N.; Shibasaki, M. *Chem. Lett.* **1991**, 1615–1618; (g) Piers, E.; Boulet, S. L. *Synlett* **1998**, 516–518; (h) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381–1396; (i) Piers, E.; Harrison, C. L.; Zetina-Roche, C. *Org. Lett.* **2001**, *3*, 3245–3247.
9. cf. Piers, E.; Renaud, J.; Retting, S. J. *Synthesis* **1998**, 590.
10. Mass spectral analysis failed to show a peak for a mono deutero or non deutero version of **9**, although the minimum detection limits of protio analogs have not been established (see implications in Ref. 12).
11. The incorporation of deuterium into the vinylic position with retention of the *Z* configuration was ascertained from proton NMR analysis. Also see Ref. 7 for the configurational stability of vinyllithium species.
12. cf. Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847–853, The only alternative explanation would invoke an extraordinarily large isotope effect from residual protio compound in **9**.
13. Since dideuterated compound **9** afforded **11** and **13** during reductive cyclization, the possibility that the primary source of reduction product arises solely from intermolecular proton tranfer to **4** via either **3** or another molecule of **4** is excluded. Our data do not exclude the possibility that the small amount of proton transfer to the vinyllithium (presumably from the butyl iodide) arises in a molecule containing an enolate, which is incapable of cyclization. The enolate would have been formed by direct deprotonation of the ketone by *n*-BuLi.