Pergamon

Tetrahedron Letters 41 (2000) 4723–4727

TETRAHEDRON LETTERS

Radical cleavage of a β-hydroxy azide: a reversal of regioselectivity in the oxidative fragmentation of hydroindoles

Peter Wipf* and David A. Mareska

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

Received 17 March 2000; accepted 26 April 2000

Abstract

Treatment of hydroindole **17** with $PhI(OAc)_2/I_2$ leads to oxidative fragmentation of the β-hydroxy azide moiety and results in the exclusive formation of keto nitrile **18** via radical cleavage of the lateral ring C–C bond.

Keywords: regioselective oxidative fragmentation; hydroxy azide; keto nitrile.

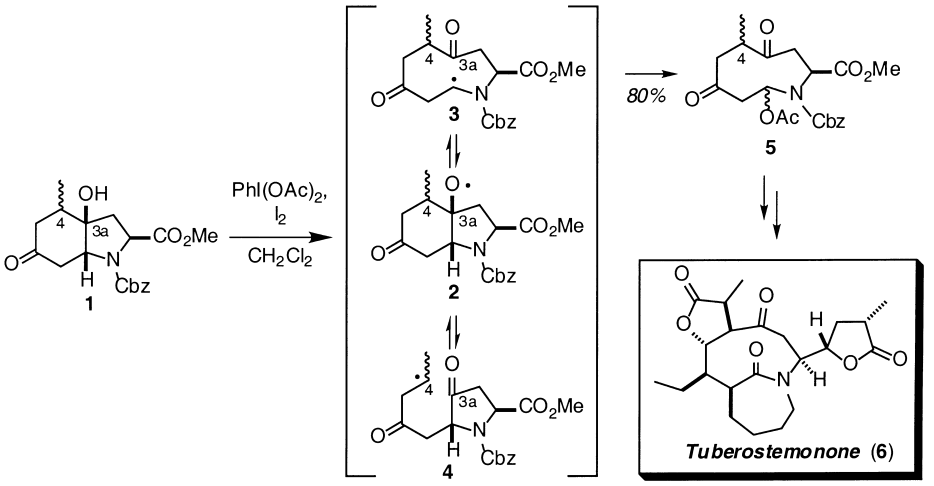
The synthesis of medium-sized rings may be accomplished by the oxidative cleavage of alkoxy radicals attached to fused bicyclic systems.[1,2] Recently, we developed new methodology for the ring expansion of 4-hydroxyhydroindoles such as **1** to azononanes in an approach toward the total synthesis of tuberostemonone **6** (Scheme 1, **1**–**5**).[3] Presumably, this conversion proceeds through a nitrogen-stabilized radical intermediate **3**. Evidence suggests that fragmentations of this type are reversible processes and that final product formation is influenced by both the stability of the radical intermediates and their relative rates of trapping.[2]

As part of our efforts to synthesize several of the biologically interesting and structurally challenging *Stemona* and *Croomia* alkaloids[4] from hydroindole **7**,[5] we envisioned directing the oxidative cleavage to afford products arising from C(3a)–C(4) bond fragmentation (Scheme 2). Such a cleavage affords an alkyl substituted pyrrolidinone that may be useful for the preparation of alkaloids such as croomine[6,7] and parvistemonine.[8] However, careful examination of the reaction mixture from oxidative fragmentation of **1** and related compounds[3] revealed no evidence of C(3a)–C(4) bond cleavage. Even after the addition of a radical stabilizing vinyl substituent at C(4) in substrate **10**, only complex product mixtures were obtained (Fig. 1). Increasing the steric bulk about the ring nitrogen (**11**) or protonating at this position (**12**) to reduce the stability of a radical analogous to **3** was similarly unsuccessful in yielding C(3a)–C(4) scission products.

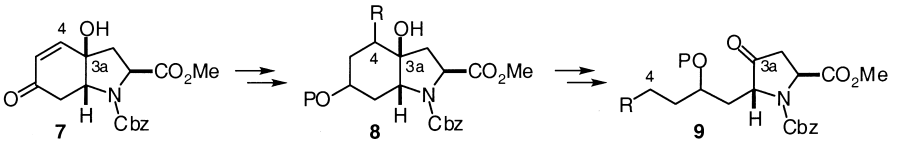
Recent studies by Suárez have shown that a radical α to an azide group is trapped by the release of nitrogen and nitrile formation.[9] From these results, we hypothesized that an azide

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00706-1



Scheme 1.



Scheme 2.

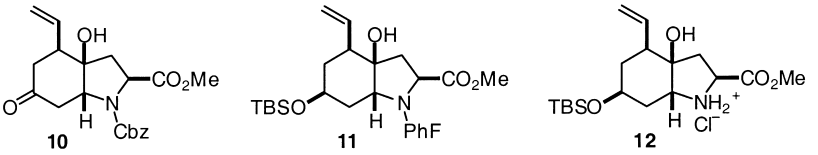
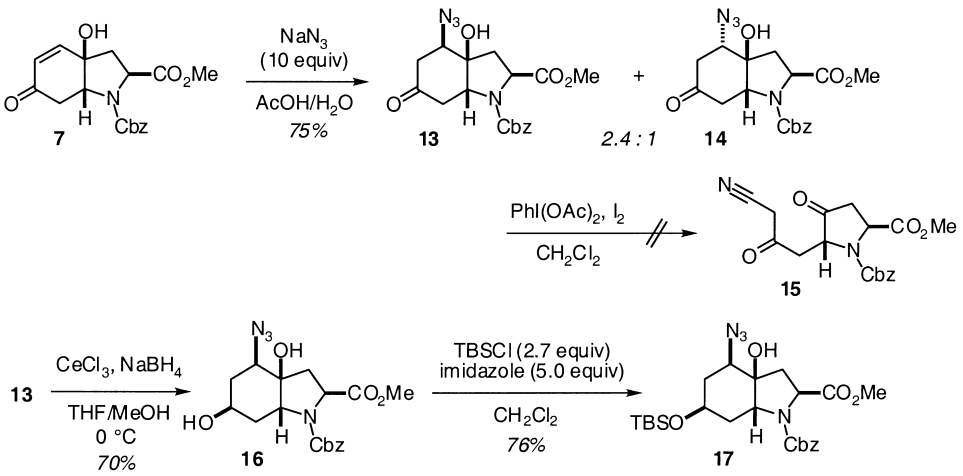


Figure 1.

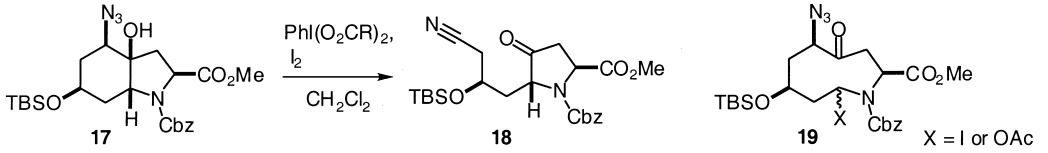
appropriately placed within a hydroindole framework may direct final product formation to arise from C(3a)–C(4) cleavage. β-Hydroxy azides suitable for probing this alternative fragmentation strategy were obtained from the conjugate addition of sodium azide to hydroindole **7** which is readily available from L-tyrosine via an oxidative cyclization process (Scheme 3).[5a] After five days, a separable mixture of isomers **13** and **14** as well as a significant amount of recovered starting material were obtained.[10] Attempts to optimize this conversion via Lewis acid mediated conjugate additions with diethylaluminum azide under anhydrous conditions failed to deliver any desired product.[11,12] Upon exposure to oxidative fragmentation conditions, both ketoazides **13** and **14** failed to afford any fragmentation product and were instead converted back to enone **7** along with decomposition products. As the presence of the carbonyl appeared to allow for facile elimination, the major isomer **13** was reduced under Luche conditions and protected as the silyl ether **17**.[13]

The oxidative fragmentation of **17** was attempted under a variety of conditions (Eq. (1)) and Table 1).[14] Treatment of **17** with iodobenzene diacetate and iodine afforded the desired ketonitrile **18** with no evidence for the formation of the transannular fragmented product **19** (entry 1). In the



Scheme 3.

absence of iodine, starting material was recovered quantitatively (entry 2). Performing the reaction at 5°C (entry 3) significantly retarded the formation of **18**. The use of iodobenzene bis(trifluoroacetate) did not effect the desired reaction and instead desilylated the starting material in almost quantitative fashion (entry 4). Lead tetraacetate also failed to yield any desired **18** (entry 5).



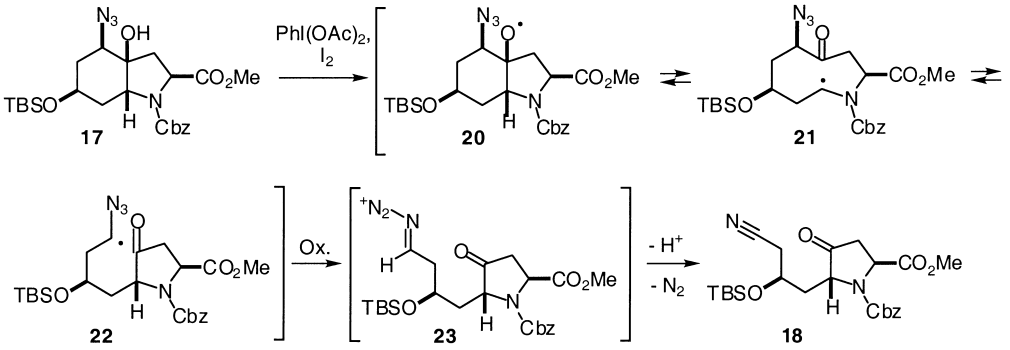
(1)

Table 1
Oxidative fragmentation of hydroxy azide **17**

Entry	Reagents	Temp. [°C]	Conc. [M]	18 [%]	Recovered Starting Material [%]
1	$PhI(OAc)_2$, I_2 (2.5 equiv)	23	0.05; CH_2Cl_2	59	10[a]
2	$PhI(OAc)_2$ (2.5 equiv)	23	0.01; CH_2Cl_2	0	quant.
3	$PhI(OAc)_2$, I_2 (2.2 equiv)	5	0.01; CH_2Cl_2	34	55
4	$PhI(O_2CCF_3)_2$, I_2 (2.5 equiv)	23	0.02; CH_2Cl_2	0	quant.[b]
5	$Pb(OAc)_4$ (4.0 equiv)	110	0.01; toluene	0	0

[a] Contaminated with an unknown byproduct; [b] Diol **16**.

The formation of **18** may be explained by an oxidative fragmentation as proposed by Suárez (Scheme 4).[9] Transannular and lateral C–C bond cleavage intermediates **21** and **22** may both be accessible from alkoxy radical **20**. Rapid and irreversible oxidation of **22** to **23** followed by elimination of N_2 provides ketonitrile **18**. An alternative, ionic mechanism involving oxidation of azide prior to C–C bond cleavage cannot be excluded, however.



Scheme 4.

In summary, we have been able to reverse the high selectivity for ring expansion previously observed in the oxidative fragmentation of hydroindoles **1** by incorporating an azide substituent at C(4) and taking advantage of the irreversible nitrogen elimination of α-azido radicals. We expect that this strategy will be generally useful in directing radical-based fragmentation processes and that the selective access toward azanonanes **5** and pyrrolidinones **18** from hydroxy indoles will further enhance the use of tyrosine oxidation products as scaffolds for natural product synthesis.

Acknowledgements

This work was supported by the National Institutes of Health (AI/GM-33506). We thank Mr. Wenjie Li for attempting the oxidative fragmentation of **10**.

References

1. (a) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. (b) Suginome, H.; Kondoh, T.; Gogonea, C.; Singh, V.; Goto, E.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 69. (c) Mihailovic, M. Lj.; Lorenc, Lj.; Pavlovic, V. *Tetrahedron* **1977**, *33*, 441. (d) Arencibia, M. T.; Freire, R.; Perales, A.; Rodríguez, M. S.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3349. (e) Boto, A.; Hernández, R.; Veláquez, S. M.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 4697. (f) Saicic, R. N. *Tetrahedron Lett.* **1997**, *38*, 295.
2. (a) Macdonald, T. L.; O'Dell, D. E. *J. Org. Chem.* **1981**, *46*, 1501. (b) Beckwith, A. L. J.; Kazlauskas, R.; Syner-Lyons, M. R. *J. Org. Chem.* **1983**, *48*, 4718. (c) O'Dell, D. E.; Loper, J. T.; Macdonald, T. L. *J. Org. Chem.* **1988**, *53*, 5225. (d) Hernández, R.; Melián, D.; Prangé, T.; Suárez, E. *Heterocycles* **1995**, *41*, 439.
3. Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576.
4. Pilli, R. A.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2000**, *17*, 117 and references cited therein.
5. (a) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739.
6. Noro, T.; Fukushima, S.; Ueno, A.; Litaka, Y.; Sakai, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1495.
7. Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.
8. Lin, W.-H.; Yin, B.-P.; Tang, Z. J.; Xu, R. S.; Zhong, Q.-X. *Acta Chim. Sin.* **1990**, *48*, 811.
9. Hernández, R.; León, E. I.; Moreno, P.; Suárez, E. *J. Org. Chem.* **1997**, *62*, 8974.
10. The relative configuration of **13** and **14** was deduced from their $J_{4,5}$ values and HMQC, HMBC, and NOE techniques. 4-(*R*)-Azido-3a-hydroxy-6-oxo-octahydro-indole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**13**). A solution of hydroindole **7** (1.0 g, 2.9 mmol) in 8 mL of MeOH, 4 mL of H_2O, and 6 mL of glacial AcOH

was cooled to 0°C and treated with NaN_3 (1.9 g, 29 mmol). The mixture was stirred at rt for 5 days, diluted with EtOAc and washed with H_2O and brine. The aqueous layer was extracted with EtOAc. The organic layers were dried ($MgSO_4$), filtered, and chromatographed on SiO_2 (1.5:1, EtOAc:hexanes) to afford 125 mg (13%) of **7**, 600 mg (53%) of **13** and 250 mg (22%) of **14** as waxy solids: compound **13**: $[\alpha]_D$ –42.3 (*c* 1.0, $CHCl_3$); IR (neat) 3434 (br), 2108, 1708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 5.23–5.19 (m, 1H), 5.09 and 4.99 (2 d, 1H, $J = 12.1$ Hz), 4.91 and 4.51 (2 bs, 1H), 4.51–4.45 (m, 1H), 4.30 and 4.18 (2 dd, 1H, $J = 7.3$ Hz), 4.14 and 4.08 (2 dd, 1H, $J = 5.3$, 11.9 Hz), 3.88 and 3.58 (2 s, 3H), 3.04 and 2.89 (2 dd, 1H, $J = 6.4$, 15.4 Hz), 2.77–2.71 (m, 1H), 2.69–2.58 (m, 1H), 2.42–2.32 and 2.21–2.17 (m, 1H), 2.42–2.32 (m, 1H), 2.21–2.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 203.9, 175.0, 174.5, 154.4, 154.0, 135.6, 128.5, 128.4, 128.3, 128.2, 127.9, 81.4, 80.5, 67.8, 67.5, 64.1, 63.5, 61.7, 57.7, 57.6, 53.2, 52.8, 44.1, 43.0, 42.2, 41.9, 35.6, 34.3; HRMS *m*/*z* calcd for $C_{18}H_{20}N_4O_6$: 388.1383, found: 388.1368.

11. Rawal, V. H.; Zhong, H. M. *Tetrahedron Lett*. **1994**, *35*, 4947.
12. Chung, B. Y.; Park, Y. S.; Cho, I. S.; Hyun, B. C. *Bull. Korean Chem. Soc*. **1988**, *9*, 269.
13. Attempted conversion of the minor isomer **14** under analogous conditions failed to produce the expected diol and instead returned a complex mixture of products.
14. 5-(*R*)-[2-(*R*)-*tert*-Butyl-dimethyl-silanyloxy)-3-cyano-propyl]-4-oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**18**). Iodobenzene diacetate (45 mg, 0.14 mmol) and iodine (35 mg, 0.14 mmol) were added sequentially at rt to a solution of hydroxy azide **17** (27 mg, 0.054 mmol) in 1.2 mL of CH_2Cl_2. The purple solution was stirred for 3 h, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and chromatographed on SiO_2 (1:3, EtOAc:hexanes) to afford 15 mg (59%) of **18** as an oil and 3 mg (~10%) of **17** contaminated with an unknown by-product. Compound **18**: $[\alpha]_D$ –45.0 (*c* 1.0, $CHCl_3$); IR (neat) 2249, 1758, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 5H), 5.31–5.22 (m, 1H), 5.16–5.09 (m, 1H), 4.72 (d, 1H, $J = 6.2$ Hz), 4.28–4.11 (m, 2H), 3.76 and 3.53 (2 s, 3H), 2.97 (dd, 1H, $J = 6.2$, 11.2 Hz), 2.60–2.45 (m, 2H), 2.50–2.30 (m, 2H), 2.00–1.90 and 1.80–1.72 (2 m, 1H), 0.91 and 0.85 (2 s, 9H), 0.14–0.01 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 208.6, 172.2, 155.5, 154.7, 135.6, 128.6, 128.4, 117.2, 116.7, 68.1, 67.6, 65.1, 63.9, 59.3, 58.3, 55.9, 55.8, 52.7, 52.6, 39.7, 39.5, 39.4, 39.1, 26.7, 26.4, 25.6, 17.9, –4.6, –4.8; HRMS *m*/*z* calcd for $C_{24}H_{34}N_2O_6Si$: 474.2186, found: 474.2181.