Tetrahedron Letters, Vol. 34, No. 34, pp. 5413-5416, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A NOVEL, STEREOSELECTIVE SYNTHESIS OF cis-4a (S), 8a(R)-DECAHYDRO-6(2H)-ISOQUINOLONES FROM MEROQUINENE ESTERS

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Abstract. *Intramolecular cyclization of N-acylated meroquinene t-butyl esters in cold H_2SO_4 cleanly afforded cis-4a(S), 8a(R)-decahydro-6(2H)-isoquinolones with complete stereocontrol in >95% yield. Formation of the meroquinene esters from cinchona alkaloid autoxidation using an improved Doering protocol was accomplished in three steps with 85% overall yield.*

The substituted perhydroisoquinoline nucleus possessing a *syn*-ring juncture is an important pharmacophore that has seen broad utility in the development of a variety of therapeutic agents, including excitatory amino acids, thrombolytics and antiviral drug candidates.[1,2] The synthetic strategies most often employed for the construction of perhydroisoquinolines consists in cyclization of arylethyl amine precursors, with a Pictet-Spengler reaction or variation thereof. High pressure catalytic reduction of the aromatic ring affords the requisite *cis*-stereochemistry. Subsequent resolution of the enantiomers is the major drawback of this tactic, since this step is inherently late in a synthesis. Natural product utilization for stereochemical purity is one alternative to the resolution route. Herein, we describe our results on a novel, stereoselective synthesis of *cis*-decahydro-isoquinolones from meroquinene *t*-butyl esters. The meroquinene esters were uniquely prepared by a modified and improved Doering autoxidation procedure.

In 1973, Uskokovic reported on the cyclization of N-benzoyl meroquinene (1) to afford a 1 : 2.4 mixture of *cis : trans*-2-benzoyldecahydro-6(2H)-isoquinolones, 2 : 3, respectively, using neat polyphosphoric acid (PPA) (eq 1).[3] These diastereomeric enones could be easily separated by

$$\text{(ratio} = 1 : 2.4)$$
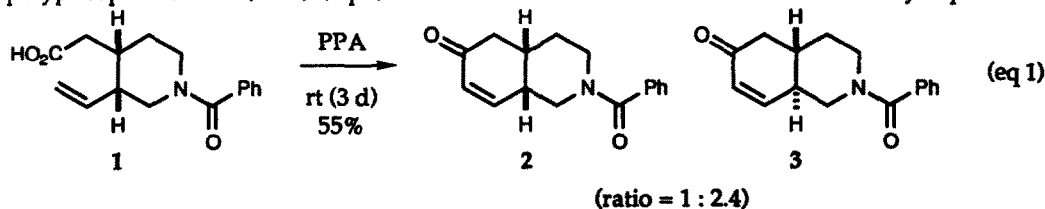
column chromatography to provide pure samples of either isomer. In order for meroquinene to be exploited as a useful building block, however, a stereoselective, non-epimerizing cyclization protocol was required. We found that the cyclization of acid 1 could be carried out in a mixture of PPA:H_2SO_4 (0 °C → 20 °C) with complete <u>cis</u>- stereocontrol in essentially quantitative yield (30 min)
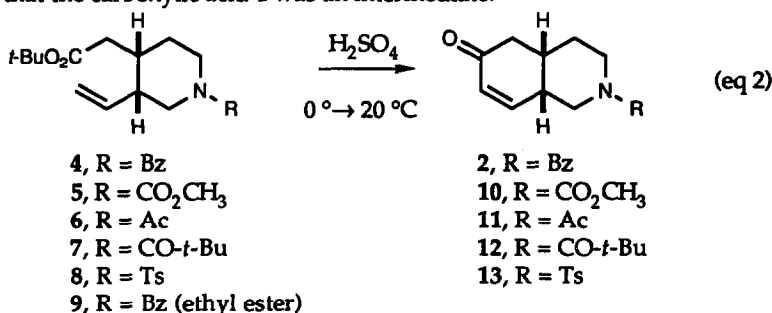
affording only *cis*-enone **2**. As might be expected, equilibration of the γ-position occurred at elevated temperatures (>25 °C). It was determined that concentrated H_2SO_4 could replace the PPA:H_2SO_4 mixture, with identical (*cis*) product profile. Trifluoroacetic anhydride (TFAA)[4] also effected the present cyclization ableit as a mixture of *cis* and *trans* enones with poor efficiency. Other acids with literature precedents[5] were attempted for the cyclization, but did not provide satisfactory results (Table).

Table. Effect of acid on cyclization and ratio.

acid	time	yield	cis:trans
PPA	120 h	55%	1:2.4
PPA/H_2SO_4	24 h	85%	1:0
H_2SO_4	1 h	98%	1:0
H_3PO_4	24 h	0%	-
HCl	18	0%	-
CH_3SO_3H	24	trace	-
$AlCl_3/CH_2Cl_2$	24 h	0%	-
TFAA	4 h	32 %	1:2
HOAc	24 h	0%	-
HNO_3	24 h	0%	-

Either pure enone **2** or **3**, when resubjected to the neat PPA reaction conditions, could be equilibrated to the same enone mixture (1 : 2.4). Equilibration was also accomplished under thermodynamic conditions, such as *p*-TsOH in THF.

N-Benzoyl meroquinene *t*-butyl ester was prepared by the autoxidation of quininone (*vide infra*), and was converted to the free carboxylic acid with NaOH.[3] Since *t*-butyl esters are readily cleaved under moderately acidic conditions,[6] we expected that sulfuric acid would accomplish deprotection as well as the desired cyclization. Thus, treating the *t*-Bu ester **4** with ice-cold H_2SO_4 effected both of the desired events, affording the enone **2** in excellent overall yield. Chromatographic analysis during the course of the reaction revealed the intermediacy of acid **1**.[7] The H_2SO_4 reaction medium was compatible with all substrates **1-8**. The reaction components (1 g substrate, 4 mL H_2SO_4,pre-cooled) were simply combined and stirred at 0 °C (30 min), then at 20 °C (30 min). The enone products were isolated by quench with ice and extraction. Attempted cyclization of N-carboxymethyl meroquinene ethyl ester (**9**) failed to afford any of the desired enone **2**, suggesting that the carboxylic acid **1** was an intermediate.

$$t\text{-BuO}_2C \quad \xrightarrow[0\,°\rightarrow 20\,°C]{H_2SO_4} \quad O= \qquad \text{(eq 2)}$$

4, R = Bz
5, R = CO_2CH_3
6, R = Ac
7, R = CO-*t*-Bu
8, R = Ts
9, R = Bz (ethyl ester)

2, R = Bz
10, R = CO_2CH_3
11, R = Ac
**12**, R = CO-*t*-Bu
13, R = Ts

TFAA and mixtures of Ac_2O with catalytic H_2SO_4 have been employed for the cyclization[4,8] of ω-olefinic acids, although the substrates studied were simple straight chain carboxylic acids that did not contain stereogenic centers. Polyphosphoric acid has also been extensively used for the acylation of alkenes at high temperatures, usually 100 °C.[9] Most ω-unsaturated carboxylic acids

involve cyclization onto an aromatic ring,[10] and examples of ω-olefinic acids are scarce. The few examples cited resulted in low yields and formation of lactone and linear dimeric by-products.[8]

Furthermore, carbonyl compounds containing available lone pairs are weak bases, and possess increased basicity due to conjugation with an olefin, as in an enone. In media such as TFAA or PPA, enones with alkyl substitution in the γ-position result in deconjugation[5] which undoubtedly proceeds through a dienolate 15 (eq 3). Sulfuric acid sufficiently protonates the enone,[11] as indicated by the inability for extraction with CH_2Cl_2 from H_2SO_4 . Following enone protonation, the conjugate base, HSO_4^-, is apparently not strong enough to deprotonate the γ-H, and maintains a strong ion pair with the enone, avoiding dienolate formation and thereby assuring the stereochemical integrity.

14   15   (eq 3)
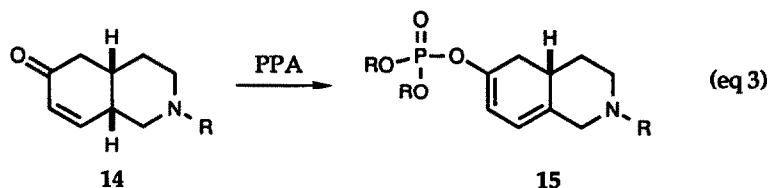
Oxidative degradation of the *cinchona* alkaloids provided the meroquinene esters employed in this study. Thus, oxidation of quinine[12] with KO-t-Bu/$Ph_2C=O$[13] in toluene afforded quininone in >95% yield. In 1946, Doering and Chanley reported on the autoxidation of quininone to meroquinene t-butyl ester in 58% yield.[14] Our modification to the Doering autoxidation procedure, which employed only t-BuOH, now includes a mixture of THF:t-BuOH (4:1) as the solvent. Substitution of the pressurized Parr bottle setup as described[14] with a simple subsurface gas addition was employed; the solvent was presaturated with oxygen gas,[15] followed by t-BuOK addition and continued O_2 gas purge. The solid quininone was then added portionwise at a rate to maintain the temperature below 25 °C.[16] Following aqueous workup, direct conversion of the organic extract to the N-acylated derivatives 4-9 provided the most expedient method for isolation of the N-acylated products, either by crystallization or chromatography. The pure esters were obtained in 65-85% yield, which avoided isolation of the polar, water soluble meroquinene esters 18. The autoxidations could also be conducted in the presence of EtOH or MeOH, thereby producing the corresponding ethyl or methyl esters (18, R' = Et, Me). Formation of these esters could occur *via* the reactive intermediate bicyclic lactam.[14]

18, Meroquinene ester   (eq 4)
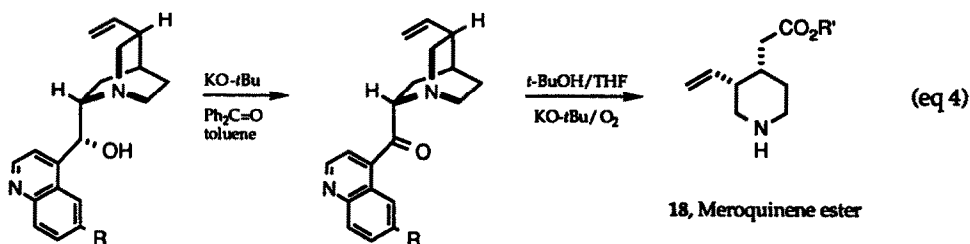
In summary, oxidative degradation of quinine provided meroquinene esters which were subsequently cyclized to *N*-acylated *cis*-decahydroisoquinolones in excellent overall yield. This unprecedented cyclization has broad mechanistic implications and methodology applications. Investigation of this reaction with other ω-olefinic acids and esters, and exploitation in total synthesis, is the subject of future research. Furthermore, with the commercial availability of quinine, high overall yields and ease of isolations, meroquinene and subsequent products are attractive members of a practical "chiral pool".

References and notes:
1. Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Paschal, J. W. *J. Org. Chem.* **1991**, *56*, 4388.
2. Houpis, I. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1993**, *34*, 2593.
3. Uskokovic, M. R.; Pruess, D. L.; Despreaux, C. W.; Shiuey, S.; Pizzolato, G.; Gutzwiller, J. *Helv. Chim. Acta* **1973**, *56*, 2834.
4. Ferrier, R. J.; Tedder, J. M. *J. Chem. Soc.* **1957**, 1435.
5. Groves, J. K. *Chem. Soc. Rev.* **1972**, *1*, 73.
6. Greene, T. W. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc.: New York, 1981, pp 168-169.
7. *t*-Butyl esters 4, 5, & 7 also cyclized directly with PPA to yield a mixture of *cis* & *trans*-enones.
8. a) Ansell, M. F.; Emmett, J. C.; Coombs, R. V. *J. Chem. Soc. C* **1968**, 217.
   b) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.
9. a) Green, A. L.; Hey, D. H. *J. Chem. Soc.* **1954**, 4306.
   b) Popp, F. D. McEwen, W. E. *Chem. Rev.* **1958**, 321.
   c) Ansell, M. F.; Brown, S. S. *J. Chem. Soc.* **1958**, 2955.
   d) Kulkarni, S. B.; Dev, S. *Tetrahedron* **1968**, *24*, 553.
   e) Conia, J. M.; Leriverend, M. L. *Bull. Chem. Soc. Fr.* **1970**, 2981, 2992.
10. a) Horning, E. C.; Walker, G. N. *J. Am. Chem. Soc.* **1952**, *74*, 5147.
    b) Green, A. L.; Hey, D. H. *J. Chem. Soc.* **1954**, 4306. Cf. also, ref. 5, 8 & 9.
11. a) Jensen, J. L.; Thibeault, A. T. *J. Org. Chem.* **1977**, *42*, 2168.
    b) Zalewski, R. I. In *The Chemistry of Enones*, Patai, S.; Rappoport, Z. Eds.; John Wiley & Sons, Inc. New York, 1989, Part 1, pp 317-354.
12. The bark of the *cinchona* tree contains a 7-8% mixture of the *cinchona* alkaloids, with quinine being the most abundant. Chemistry reviews for the *cinchona* alkaloids include:
    a) Turner, R. B.; Woodward, R. B. In *The Alkaloids. Chemistry and Physiology*; Manske, R. H. F.; Holmes, H. L. Eds.; Academic Press, Inc.: New York, 1953; Vol. III, pp 1-63.
    b) Uskokovic, M. R.; Grethe, G. In *The Alkaloids. Chemistry and Physiology*; Manske, R. H. F.; Holmes, H. L. Eds.; Academic Press, Inc.: New York, 1973; Vol. 14, p 181-223.
    c) Verpoorte, R.; Schripsema, J.; van der Leer, T. In *The Alkaloids. Chemistry and Physiology*; Brossi, A. Ed.; Academic Press, Inc.: New York, 1988; Vol. 34, pp 331-398.
13. Modified procedure from: Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425.
14. Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586.
15. Compressed air could also be used as the oxygen source.
16. When the temperature was allowed to exceed 35 °C, a second meroquinene ester was isolated and characterized as the *i*-propyl ester. The formation of this by-product is under investigation.