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Chemoselectivity of the Ruthenium-Catalyzed Hydrative Diyne Cyclization: Total Synthesis of (+)-Cylindricine C, D, and E

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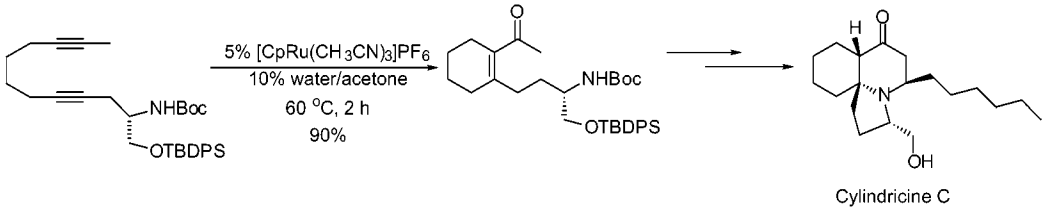
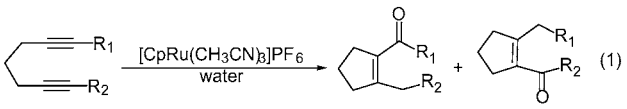
ABSTRACT



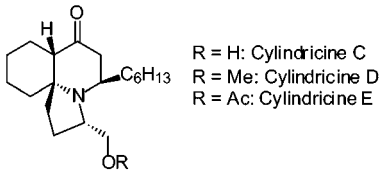
The chemoselectivity of the ruthenium-catalyzed hydrative diyne cylization is explored in an expeditious synthesis of the tricyclic alkaloids cylindricine C, D, and E.

As part of an ongoing study of the ability to effect a hydrative cyclization of diynes to acylcycloalkenes,[1] the question of the chemoselectivity with unsymmetrical diynes arises (eq 1). In addressing this important issue, the impact of conjugation, wherein one of the R groups would be vinyl, was particularly intriguing because electronic versus steric effects might be anticipated to operate in opposing directions.



(1)

Among a group of structurally interesting secondary metabolite alkaloids isolated from various ascidians, including clavepictines,[2] fasicularin,[3] and lepadiformine,[4] stand cylindricines A−J. These tricyclic alkaloids were isolated by Blackman[5] from *Clavelina cylindrical*, a marine benthic invertebrate (ascidian) found off the coast of Tasmania. Cylindricine C, D, and E appeared to represent an attractive context in which to explore this question.



Crude cylindrincine extracts have shown some biological activity in a brine shrimp bioassay,[5] whereas other members of this family have activity against a DNA-repair-deficient yeast strain[3] and inhibit growth of murine leukemia and human solid tumor cell lines.[2] The absolute configurations of natural cylindricine C, D, and E are unknown, and the optical rotations were not reported. Cylindricine C has been

(1) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516.

(2) Raub, M. F.; Cardelina, J. H., II; Choudhary, M. I.; Ni, C.-Z.; Clardy, J.; Alley, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 3178.

(3) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363.

(4) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauternen, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *34*, 686.

(5) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. H. *Tetrahedron* **1993**, *49*, 8645. (b) Blackman, A. J.; Li, C. *Aust. J. Chem.* **1994**, *47*, 1355. (c) Blackman A. J.; Li, C. *Aust. J. Chem.* **1995**, *48*, 955.

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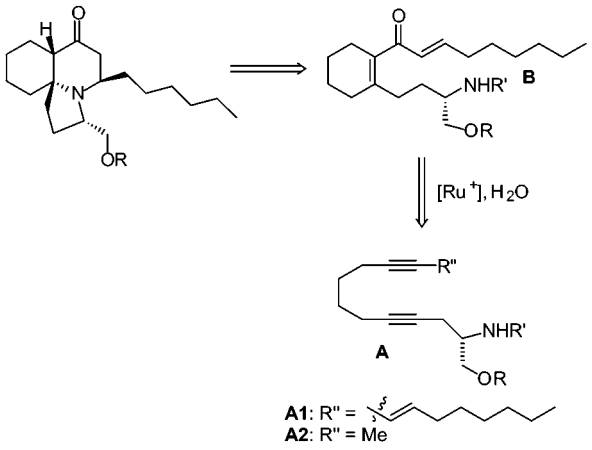
made once previously[6] starting from a chiral triol, and the racemic synthesis of cylindricines D and E has also been completed.[7]

As illustrated in Scheme 1, it was envisioned that a double

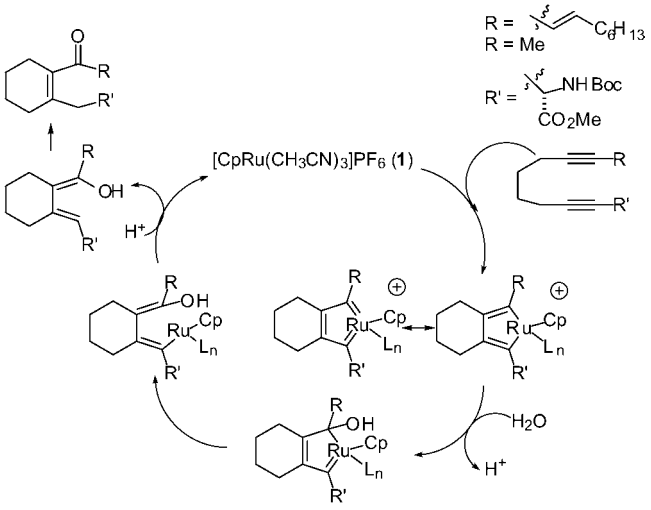
Scheme 1. Cylindricine Retrosynthesis



conjugate addition of a pendant amine onto an appropriately situated divinyl ketone would allow expeditious entry into the tricyclic core of the cylindricines. Although a similar endgame was utilized by Molander,[6] we hoped to exploit the versatility of the novel hydrative diyne cyclization recently developed in our laboratory[1] to access the functionalized amino divinyl ketone core in a rapid fashion.

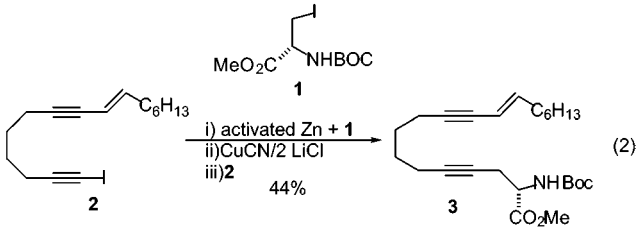
The key step in the synthesis is the ruthenium-catalyzed hydrative cyclization of intermediate **A** to **B**. The proposed mechanism of this reaction is shown below and involves water addition to a ruthenacyclopentadiene or -cyclopentatriene (Scheme 2). Intermediate **B** could be made directly if **A1** (R″ = heptenyl) could be chemoselectively cyclized with water attack occurring only at the top and presumably least hindered alkyne.[8] As an alternative, **A2** (R″ = methyl)

Scheme 2. Mechanistic Proposal

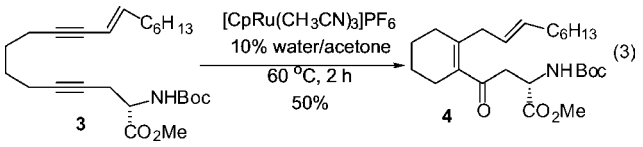


may function well in the reaction on the basis of experience gained in the methodological development of the reaction.[1] The resulting methyl ketone could then be readily transformed into **B** through an aldol condensation reaction. The diastereoselective double conjugate addition would then give the core of the cylindricines with the existing chiral center controlling the selectivity of the other three.

In the forward direction, the cyclization precursor **A1** was prepared from serine iodide **1**[9] and enediyne **2**[10] utilizing the alkyl copper−zinc/haloalkyne chemistry developed by Knochel[11] (eq 2).



With compound **3** in hand, the ruthenium-catalyzed hydrative diyne cyclization was carried out under standard conditions. Interestingly, a single cyclization product formed that proved to be the isomer, which would not be productive for the cylindricine synthesis (eq 3).

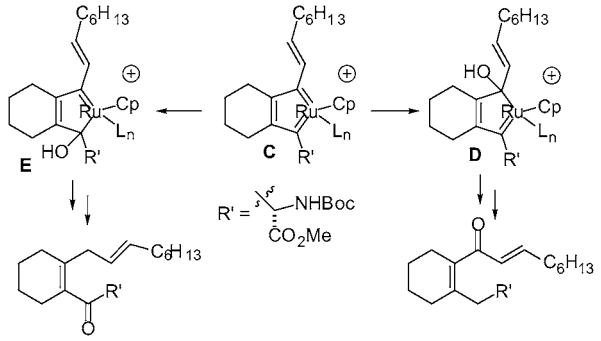


Although previous data[1] indicated that steric effects were the chief factor in determining chemoselectivity and a vinyl group is generally viewed as smaller than a β-branched alkyl chain,[12] it appears other factors can influence the selectivity as well. It is possible that disruption of conjugation developed in the proposed ruthenacyclopentadiene or cyclopentatriene (**C**, Scheme 3) going to adduct **D** disfavors attack at the alkyne adjacent to the vinyl group. Thus, the addition of water favors formation of adduct **E**, which is the precursor of the observed product.

As indicated above, the alternative strategy was to perform the hydrative cyclization on the methyl alkyne, followed by an aldol condensation. This example competes the differential steric effects versus the prospect of amide participation. Previously, we have noted a cyclization involving a tethered

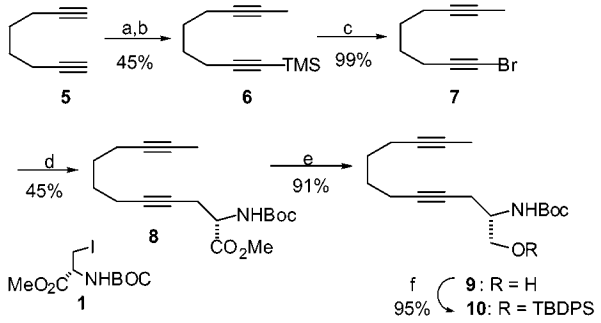
(6) Molander, G. A.; Ronn, M. *J. Org. Chem.* **1999**, *64*, 5183.
(7) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630.
(8) Previous development indicated that the attack of water occurs at the least hindered alkyne.
(9) Compound **1** is prepared in three steps (methyl ester formation, Boc protection, iodination) from serine in 60% overall yield (see Supporting Information).
(10) Compound **2** is prepared from 1,7-octadiyne and the vinyl iodide derived from 1-octyne (DIBAL-H, I_2) using standard Sonagashira coupling followed by iodination with *n*-BuLi and I_2 in 40% overall yield (see Supporting Information).
(11) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799.
(12) (a) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1966**, *31*, 894. (b) Eliel E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

Scheme 3. Rationale for Formation of Undesired Isomer



hydroxyl nucleophile.[1] The synthesis of the desired cyclization precursor was carried out in a straightforward manner starting from readily available compounds (Scheme 4).

Scheme 4. Synthesis of Cyclization Precursor[a]

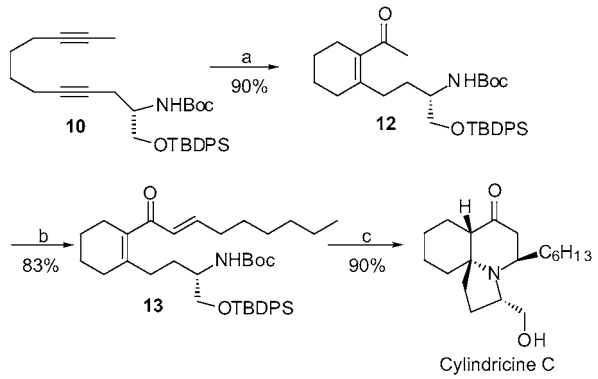


[a] (a) LHMDS, TMS-Cl; (b) *n*-BuLi, CH_3I; (c) 10% $AgNO_3$, NBS, DMF; (d) (i) activated Zn + **1**, (ii) CuCN/2 LiCl, (iii) **7**; (e) $LiBH_4$; (f) TBDPS-Cl, imidazole, DMF.

Monosilylation of 1,7-octadiyne proceeded in moderate yield with the remainder of mass being bisilylated product and starting material. This intermediate was then methylated in quantitative yield, and the alkynyl-TMS group was converted into an alkynyl bromide[13] in one step to give the diyne coupling precursor **7** in 44% yield over three steps. Serine-derived iodide **1** was then coupled to **7** using the Knochel copper−zinc reagent[11] in moderate yield. The remainder of the mass was predominately the serine-bromide and alkyne resulting from halogen−metal exchange. Use of the alkynyl iodide led to a much lower yield because of increased exchange, whereas the alkynyl chloride did not react. Other attempts to optimize this reaction did not lead to any increase in yield. The ester group was then selectively reduced with $LiBH_4$, and the primary alcohol was protected as the TBDPS ether to produce the cyclization precursor **10** in six steps.

The ruthenium-catalyzed hydrative diyne cyclization was carried out with 5% $[CpRu(CH_3CN)_3]PF_6$ (**11**) in 10 vol % water/acetone at 60 °C to give α,β-unsaturated ketone **12** in 90% yield (Scheme 5). Only a trace amount of the undesired

Scheme 5. Hydrative Diyne Cyclization and Completion of Cylindricine C[a]



[a] (a) 5% **11**, 10% water/acetone, 60 °C, 2 h; (b) (i) LDA, heptanal, (ii) MsCl, Et_3N; (c) (i) TFA, DCM, (ii) K_2CO_3, PhMe reflux, (iii) TBAF.

isomer was detected. Diyne **8** also participated in the cyclization to deliver a single product of the same chemoselectivity as **10**. However, it was desirable to reduce the ester prior to cyclization in order to avoid potential ketone reduction. Catalyst **11** has previously been shown to deprotect unhindered TBS groups; however, no sign of TBDPS cleavage was observed in the cyclization of **10**. A standard LDA-mediated aldol reaction was then carried out between methyl ketone **12** and heptanal. The crude reaction mixture was directly submitted to elimination (MsCl, Et_3N) without prior purification to give divinyl ketone **13** in 83% yield. The double conjugate addition occurred readily upon cleavage of the Boc group with TFA/DCM and free-basing (NaOH/DCM) the TFA-salt of the resulting primary amine. On a small scale the double cyclization occurred directly to give a moderate yield of the TBDPS-protected cylindricine C along with the monocyclized adduct.

On a larger scale, refluxing the mixture of amines with potassium carbonate in toluene at reflux for 68 h[14] led to nearly complete conversion to the protected cyclindricine C, which could be isolated in 90% yield. The TBDPS group was then removed with TBAF in THF to give a quantitative yield of cylindricine C, whose spectra matched the natural product. The rotation ($[\alpha]^{25}_D$ +61 (c = 0.4, CH_2Cl_2)) was opposite in sign of that reported by Molander[6] ($[\alpha]^{25}_D$ −64 (c = 0.2, CH_2Cl_2)) as expected.

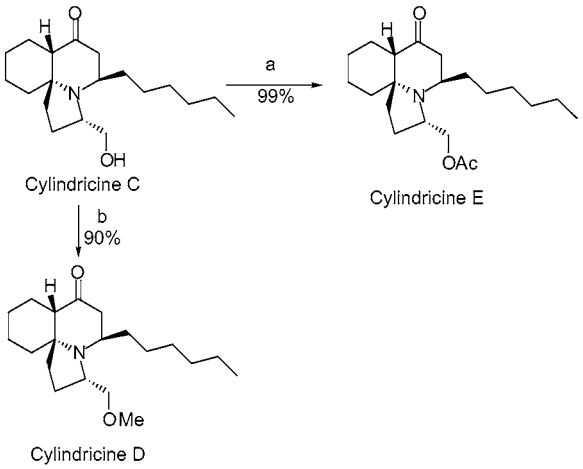
Cylindricine C could then be transformed into cyclindricine D and E in a straightforward manner. Acylation proceeded in quantitative yield to give cyclindricine E, whereas methylation produced cyclindricine D in 90% yield (Scheme 6).

In conclusion, we have shown the utility of the ruthenium-catalyzed hydrative diyne cyclization to transform unsym-

(13) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994** 485.

(14) The time required for cyclization seemed to vary somewhat, with larger scale reactions taking longer times.

Scheme 6. Conversion of Cylindricine C into D and E[a]



[a] (a) Ac_2O, Et_3N, DMAP, DCM; (b) MeI, Ag_2O, CH_3CN, 3 d.

metrical diynes into a single regioisomeric vinyl ketone product. It appears the both steric and conjugation factors play significant roles in determining the chemoselectivty. The vinyl ketone intermediate was then transformed into cylindricine C in 9 steps, and cylindricine D and E in 10 steps from commercially available 1,7-octadiyne.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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