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A New Radical-Based Route to Calothrixin B

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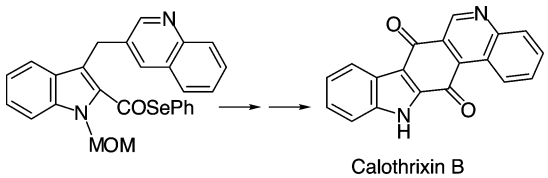
ABSTRACT

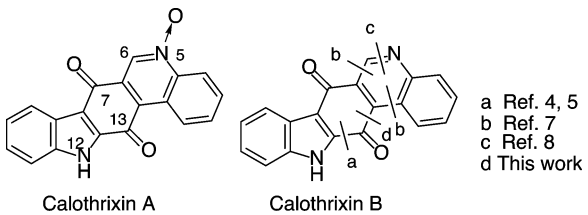


Calothrixin B

A high-yielding totally regioselective intramolecular homolytic acylation of a quinoline ring constitutes the key step in a new synthesis of the pentacyclic indolo[3,2-*j*]phenanthridine alkaloid calothrixin B.

Calothrixin B and its *N*-oxide derivative (calothrixin A) are quinone-based natural products isolated in 1999 from the cyanobacteria *Calothrix*[1] that display potent antimalarial and anticancer properties.[2] Owing to their striking biological activities as well as their pentacyclic indolo[3,2-*j*]phenanthridine skeleton, unprecedented among natural products,[3] calothrixins have attracted the synthetic interest of several research groups. Thus, four syntheses of calothrixins have been reported to date relying on the strategies depicted in Figure 1. In 2000, Kelly et al.[4] and two years later Chai et al.[5] synthesized calothrixin B and A by taking advantage of elegant metalation techniques, inspired in earlier syntheses of ellipticine quinones,[6] to assemble the indole and the quinoline nucleus (last bond formed $C_{12a}-C_{13}$, bond a). More recently, Guingant et al.[7] and Hibino et al.[8] accomplished the synthesis of calothrixin B by means of completely different strategies, such as a hetero-Diels−Alder reaction (bonds C_6-C_{6a} and $C_{13a}-C_{13b}$, bonds b) and a final formation of the quinoline ring from an appropriately substituted carbazole (bond C_5-C_6, bond c), respectively. In this context, we envisaged an alternative approach to the pentacyclic skeleton of calothrixin B, in which the central carbocyclic ring would be closed in the last synthetic steps by homolytic acylation of the 4-position of the quinoline ring (bond formed $C_{13}-C_{13a}$, bond d). In this manner, an electron-deficient quinoline ring would react with a nucleophilic acyl radical,[9] which could be considered as the umpolung of the intramolecular Friedel−Crafts acylation.

Intramolecular homolytic aromatic substitutions by nucleophilic carbon-centered radicals have become an important



Calothrixin A Calothrixin B

Figure 1. Calothrixins. Synthetic strategies.

(1) Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, J.; Saliba, K. J.; Smith, G. D. *Tetrahedron* **1999**, *55*, 13513−13520.
(2) Bernardo, P. H.; Chai, C. L. L.; Heath, G. A.; Mahon, P. J.; Simith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958−4963 and references therein.
(3) For a previous approach to the pentacyclic system of calothrixins, see: Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939−1946.
(4) Kelly, T. R.; Zhao, Y.; Cavero, M.; Torneiro, M. *Org. Lett.* **2000**, *2*, 3735−3737.
(5) (a) Bernardo, P. H.; Chai, C. L. L.; Elix, J. A. *Tetrahedron Lett.* **2002**, *43*, 2939−2940. (b) Bernardo, P. H.; Chai, C. L. L. *J. Org. Chem.* **2003**, *68*, 8906−8909.
(6) (a) Watanabe, M.; Snieckus, V. *J. Am. Chem.* Soc. **1980**, *102*, 1457−1460. (b) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451−5457.

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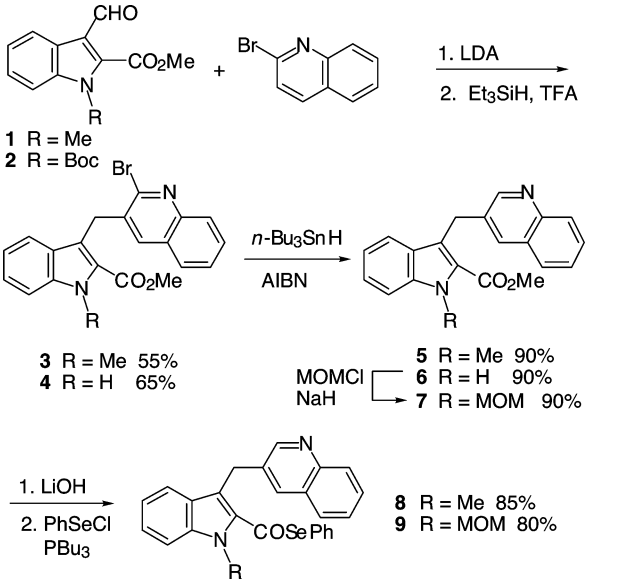
tool for the construction of otherwise quite inaccessible substituted heterocycles.[10,11] However, to our knowledge, the use of quinolines as substrates in intramolecular processes has been limited to the reaction with aryl radicals under reductive (tributyltin hydride) conditions.[12] In fact, most reported examples deal with intermolecular reactions conducted in acidic media under oxidative protocols.[13]

In the past few years, we have been studying the generation of 2-indolylacyl radicals from the corresponding phenyl selenoesters and their reaction with alkenes under reductive conditions.[14] Cyclization upon aromatic rings was also possible,[15] but under nonreductive (hexabutylditin/*hν*) conditions, producing benzocarbazoledione[16] and ellipticine quinones[17] in moderate yields. Based on these results, we expected that the related quinoline-containing radicals would participate in similar cyclizations, ultimately leading to the carbazoledione moiety characteristic of calothrixin B.

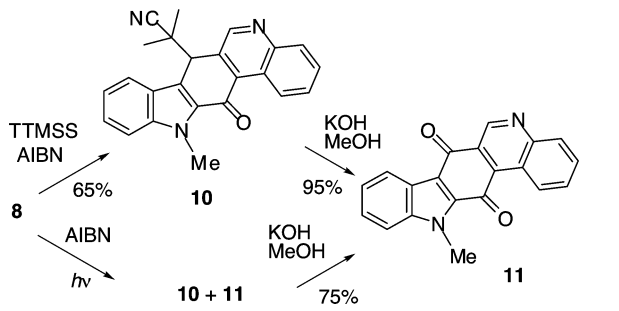
Our investigation began with the preparation of selenoester **8**, a model radical precursor bearing the required (3-quinolyl)methyl moiety connected to the indole 3-position.[18] This compound was easily accessible from *N*-methylindole **1** as depicted in Scheme 1. Chemoselective reaction with 3-lithio-2-bromoquinoline, followed by triethylsilane reduction of the resulting carbinol provided 2-bromoquinoline **3**, which was converted into methyl ester **5** upon reduction. Subsequent hydrolysis of **5**, followed by phenylselenation of the respective carboxylic acid gave the target compound **8**.

Scheme 1. Preparation of the Radical Precursors



N-Methylselenoester **8** was first allowed to react under conditions similar to those reported in our earlier work, i.e., with *n*-Bu_6Sn_2 under 300 W sun lamp irradiation. However, after irradiation and heating at 80 °C for 24 h, we obtained a complex reaction mixture of unidentified products, the expected quinone only being detected in trace amounts. As this disappointing result might be related with an increased reactivity of the quinoline with respect to the pyridine or phenyl rings, we turned to reductive conditions, hoping that the cyclization would now be fast enough to avoid the premature reduction of the initially formed acyl radical. We were pleased to find that treatment of selenoester **8** with tris(trimethylsilyl)silane[19] (TTMSS) and azobisisobutyronitrile (AIBN, 2.5 molar equiv) at 80 °C for 8 h led to the calothrixin-related pentacycle **10** in 65% isolated yield (Scheme 2). The rather surprising structure of **10**, incorporating the 2-cyano-2-propyl moiety of the initiator, was

Scheme 2. Cyclization in the *N*-Methyl Series



(7) Sissouma, D.; Collet, S. C.; Guingant, A. Y. *Synlett* **2004**, 2612−2614.

(8) Tohyama, S.; Choschi, T.; Matsumoto, K.; Yamabuki, A.; Ikegata, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett*. **2005**, *46*, 5263−5264.

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(12) (a) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*. **2001**, *42*, 2907−2910. (b) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387−3400. For a review, see: (c) Harrowven, D. C.; Sutton, B. J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2004; Vol. 16, pp 27−53.

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(14) (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *Org. Lett*. **2001**, *3*, 1697−1700. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem*. **2001**, *66*, 7547−7551. (c) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Org. Lett*. **2004**, *6*, 759−762.

(15) For previous cyclizations of acyl radicals upon indoles and pyrroles under *n*-Bu_3SnH−AIBN conditions, see: (a) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett*. **1999**, *40*, 7153−7157. (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2001**, *42*, 7887−7890.

(16) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Tetrahedron. Lett*. **2004**, *45*, 5605−5609.

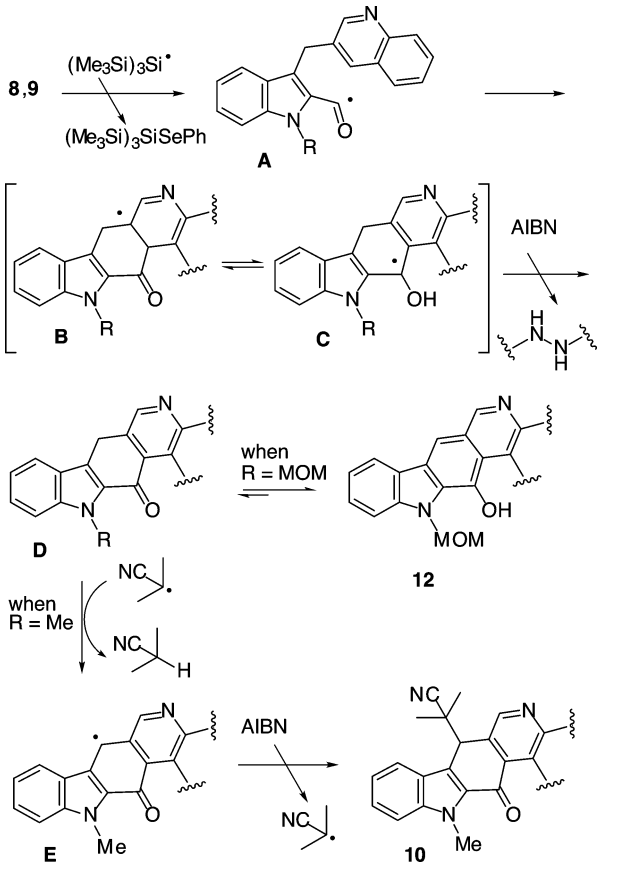
(17) Bennasar, M.-L.; Roca, T.; Ferrando, F. *J. Org. Chem*. **2005**, *70*, 9077−9080.

(18) The placement of a carbonyl group in the tether chain was discarded as it would probably diminish the reactivity of the acyl radical.

established by a combination of HSQC and HMBC experiments. As expected, **10** could be converted into *N*-methylcalothrixin (**11**) by treatment with KOH in MeOH, through a process involving a gramine-type nucleophilic substitution (elimination−addition via a 3-alkylideneindolenine) and the spontaneous oxidation of the resulting carbinol (95% yield).

Formation of pentacycle **10** was consistent with the radical addition−rearomatization−overoxidation sequence depicted in Scheme 3. Thus, the initially formed radical **A**, coming

Scheme 3. Probable Mechanism



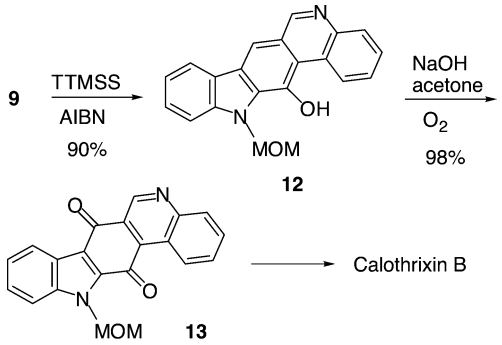
from the abstraction of the phenylseleno group by the silyl radical, undergoes regioselective cyclization upon the 4-position of the quinoline ring to give the azacyclohexadienyl radical **B**. Considering the numerous precedents of homolytic aromatic substitutions under apparently reductive conditions,[10,11] this radical (or the tautomeric benzhydryl radical **C**) is probably oxidized by hydrogen-atom abstraction at the hands of the initiator AIBN.[20,21] A new hydrogen-atom abstraction at the doubly benzylic position of pentacycle **D**, for instance by 2-cyano-2-propyl radicals, would lead to the radical **E**, which would be intercepted by AIBN.[22]

In the above sequential events leading to **10**, TTMSS would only participate in the initial generation of the 2-indolylacyl radicals. So, we wondered if we could promote a metal-free[23] homolytic sequence in the presence of AIBN acting as the oxidant, accomplishing the initial homolysis of the C−Se bond under simple irradiation.[9,24] Our reasoning proved to be correct as cyclization did take place when selenoester **8** and AIBN were irradiated (300 W sun lamp) at 80 °C in benzene.[25] Consumption of the starting product required longer reaction times (12 h) than under the above reductive conditions and the slow addition of higher amounts of the reagent (0.5 molar equiv every 1.5 h up to a total of 4 molar equiv).[26] Interestingly, after the extractive workup the crude reaction product was shown by ^{1}H NMR to be a 1:1 mixture of the pentacycle **10** and *N*-methylcalothrixin (**11**), thus indicating that complete oxidation to the quinone system had taken place under the reaction conditions. Treatment of this mixture with KOH in MeOH as above allowed the isolation of **11** in 75% overall yield from **8**.

At this point, access to the natural product calothrixin B required the extension of the chemistry outlined above to a radical precursor suitably protected at the indole nitrogen. To this end, we focused our attention on *N*-(methoxymethyl)-selenoester **9**, which was prepared from indole **2** by a synthetic route parallel to that previously used in the model series (Scheme 1). The overall yield through synthetic intermediates **4**, **6**, and **7** was 42%.

To our delight, *N*-MOM-substituted 2-indolylacyl radicals generated from selenoester **9** under reductive conditions (TTMSS, AIBN, 2 molar equiv, 80 °C, 4 h) underwent cyclization with an even higher efficiency than their *N*-methyl counterparts. Nevertheless, the reaction followed a different course since pentacyclic phenol **12**, a fully aromatic tautomeric form of **D** (R = MOM, Scheme 3) was isolated in a yield as high as 90% (Scheme 4).[27] The reaction was clean

Scheme 4. Synthesis of Calothrixin B



and showed no indication of byproducts coming from either the alternative mode of addition at the quinoline 2-position or overoxidation. On the other hand, upon application of the

(19) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.

(20) For a discussion, see: Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95−98 and references therein.

(21) Azo compounds have been shown to abstract hydrogen from the benzhydryl radical to yield benzophenone and hydrazines: Engel, P. S.; Wu, W.-X. *J. Am. Chem. Soc.* **1989**, *111*, 1830−1835.

(22) For the isolation of AIBN-containing byproducts in related radical cyclizations, see: (a) Bennasar, M.-L.; Roca, T.; Griera, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 6268−6271. (b) See also ref 14b.

AIBN/sun lamp irradiation protocol phenol **12** was also isolated as the only product, although in a lower yield (50%).

Clearly, AIBN (or 2-cyano-2-propyl radicals) is not able to overoxidize the initially formed cyclization product in this series, i.e., phenol **12**, which would be in the most favored tautomeric form, perhaps because of the establishment of a hydrogen bond between the hydroxy and methoxy group. From the synthetic standpoint, this was not a serious limitation since phenol **12** could be converted in a nearly quantitative yield into *N*-MOM calothrixin (**13**), a known immediate precursor of calothrixin B,[4,5] by mild oxidation with molecular oxygen in basic medium.[28]

(23) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082.

(24) For the generation of acyl radicals by photolysis of acyl tellurides, see: Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937−8951.

(25) No cyclization was observed when selenoester **8** was irradiated at 80 °C without AIBN or when heated in the presence of AIBN without irradiation.

(26) The half-life for decomposition of AIBN is 2 h at 80 °C: Walling, C. *Tetrahedron* **1985**, *41*, 3887−3900.

(27) The use of *n*-Bu_3SnH instead of TTMSS led to phenol **12** in a lower yield (70%).

(28) For related oxidations in basic medium, see: (a) Asche, C.; Frank, W.; Albert, A.; Kucklaender, U. *Bioorg. Med. Chem.* **2005**, *13*, 819−837. (b) Tao, Z.-F.; Sowin, T. J.; Lin, N.-H. *Tetrahedron Lett.* **2005**, *46*, 7615−7618.

In conclusion, we have shown that the cyclization of 3-(3-quinolyl)methyl-2-indolylacyl radicals under TTMSS−AIBN conditions provides an efficient synthetic entry to calothrixin-related pentacycles, which are obtained in a different oxidation state depending on the substitution at the indole nitrogen. The reactions can also be performed under a new metal-free protocol that illustrates the determinant role of AIBN in homolytic aromatic substitutions. Starting from *N*-MOM substrates, we have accomplished a new synthesis of calothrixin B, thus highlighting the strong potential of cyclizations of 2-indolylacyl radicals upon aromatic systems for the construction of polycyclic indole compounds.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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