JOC Article

Total Synthesis of (+)- and (−)-Duryne: A Potent Anticancer Agent from the Marine Sponge Cribrochalina Dura. Establishment of the Central Double Bond Geometry and the Absolute Configuration of the Chiral Centers

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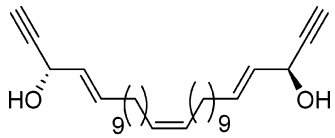

(*S*)-(+)-Duryne

Duryne is a C30 polyacetylenic alcohol with *C*2 symmetry. Despite its potent cytotoxicity, its central double bond geometry and the absolute configuration of the chiral centers were not determined. We report the total syntheses of both enantiomers of the anticancer natural product (+)-duryne and the establishment of its stereochemistry by synthesizing both geometric isomers. The natural (+)-duryne is identified as (15*Z*) and (3*S*,28*S*) as shown in structure **1**. The autoxidation/Wittig coupling reaction was employed to synthesize the central (Z)-olefin. The stereochemistry of the (*E*)-alkene isomer was constructed stereoselectively by using $LiAlH_4$ reduction of the corresponding alkyne. The absolute configurations of the chiral centers are established by using Burgess' enzymatic resolution procedure with Pseudomonas AK lipase.

Introduction

Duryne was isolated in 1987 from the marine sponge *Cribrochalina dura* by Wright and co-workers.[1] It was found that duryne inhibits the growth of several human tumor cell lines including leukemia, colon, lung, gastric, and breast cancers. It exhibits an IC_{50} of 0.07 μg/mL against p388 murine leukemia, and minimum inhibitory concentrations of 0.1 μg/mL against other human tumor cell lines. However, the geometry of the central $C^{15}{=}C^{15'}$ olefin and the absolute stereochemistry of the chiral centers were not determined.[2] Two previous synthetic studies have been published. None was able to correlate the stereochemistry of the synthetic sample with the natural duryne. The first study by Deshpande produced racemic mixtures of duryne.[3] The second study by Sharma and Chattopadhyay utilized the monoprotected diacetylene alcohol to prepare the (*15E*,*R*,*R*)-isomer of duryne.[4] The *C*2 symmetry of the molecule renders the two protons on the central double bond equivalent; hence no indicative coupling constant is available. All other spectroscopic data seem to provide no definite conclusions.

In recent years, we have been involved in the total synthesis of biologically active acetylenic alcohols and have reported the syntheses of several polyacetylene natural products.[5−8] We set out in this study to establish the configuration of the central double bond and the absolute configurations of the stereocenters

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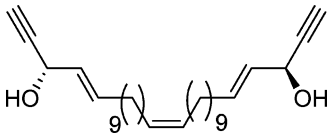

FIGURE 1. Anticancer agent, natural (*S*)-(+)-duryne, from the marine sponge *Cribrochalina dura.*

for the natural duryne. We are pleased to report a successful correlation of our synthetic sample and the reported data for the natural duryne.

Results and Discussion

Our synthetic effort started with the known (Z)-alkene diol (**2**),[9,10] which was prepared in three steps from the commercially available ω-bromoundecanoic acid, Scheme 1. The ω-bromoacid was converted to the corresponding methyl ester, which was treated with Ph_3P in acetonitrile to yield the phosphonium salt, using a reported procedure.[11] The (*Z*)-geometry of the central double bond was established by the autoxidation of the Wittig reagent generated in situ as reported by Poulain and co-workers.[9] Oxygen was bubbled through the mixture during the reaction as reported by Capon.[12] The diol **2** was converted to the dialdehyde **3** through a two-step sequence: (1) PCC oxidation to the corresponding dialdehyde and (2) Wittig reaction of the dialdehyde with $Ph_3P{=}CHCHO$ to yield dial **3**. The addition of acetylenic magnesium bromide reagent to dial **3** produced the precursor **4** for enzymatic resolution.

The general procedures of Burgess were followed using lipase AK from *pseudomonas sp* for the enzymatic resolution of the acetylenic alcohol **4**.[13,14] The progress of the reaction was followed by both thin layer chromatography and ^{1}H NMR to ensure a clean kinetic resolution of the enantiomers. The separation of the diacetate **5**, monoacetate **6**, and the diol **7** was done by column chromatography. Diol **7** has a melting point of 41−42 °C and an optical rotation of $[\alpha]_D$ −26.3. The removal of the acetate group from **5** yields diol **1**, which gives an optical rotation of $[\alpha]_D$ 27.1 and a melting point of 43−45 °C. These values are very close to those reported[1] for the natural duryne: $[\alpha]_D$ 29 and 44−45 °C. In a study of enzymatic resolution of secondary alcohols by the lipases from *Pseudomonas* sp. Burgess proposed a simple active site model for predicting enantioselectivity.[13] This model predicts that alcohols resolved most efficiently have one small and one relatively large group attached to the hydroxylmethine functionality. Duryne is similar in structure to adociacetylene, which we have successfully resolved using lipase from *Pseudomonas* sp.[15] For most secondary alcohols, the rate of acylation is faster for the (*R*)-configuration than for the (*S*)-configuration. However, for the acetylenic alcohol **4** the alcohol with (*S*,*S*) configuration is acylated faster because the small acetylenic group has a higher priority in the nomenclature system. From these considerations and the data obtained, we surmise that the natural duryne has a (*Z*)-central double bond and (*S*,*S*)-configurations at the chiral centers. However, in order to remove the doubt that the corresponding isomer with a central (*E*) double bond might have a similar optical rotation, we decided to synthesize the (*E*)-isomer and resolve the racemic mixture as well.

The (*E*)-geometry of the central double bond of the trans isomer was constructed with $LiAlH_4$ reduction of an internal alkyne precursor.[3] The racemic mixture of the (*E*)-isomer **8** was prepared following the procedures by Deshpande.[3] After enzymatic resolution of **8** the optical activity obtained for the (15*E*), (3*S*,28*S*)-diol **12** is $[\alpha]_D$ 13.8 and that for the (15*E*), (3*R*,-28*R*)-diol **11** is $[\alpha]_D$ −13.0. Thus by synthesizing both geometric isomers of duryne and the subsequent enzymatic resolution, we conclude that the natural (+)-duryne reported by Wright et al. has a central double bond geometry of (*Z*) and absolute configuration of (*S*,*S*) as shown in structure **1**. This conclusion not only is consistent with all experimental data reported in this study, but it is also consistent with several known *C*2 symmetric acetylenic alcohols isolated from marine sources.[16−19] They are listed in Table 1 for comparison purposes.

Summary

The central olefin geometry and the absolute configuration of the potent anticancer polyacetylenic alcohol natural (+)-duryne have been established. Through the total syntheses of both (*Z*) and (*E*) isomers and the subsequent enzymatic resolution of each racemic mixture, natural duryne is identified as (15*Z*) and (3*S*,28*S*) as shown in structure **1**. This conclusion is consistent with naturally occurring *C*2 symmetric acetylenic alcohols from marine sources.

Experimental Section

Triaconta-2*E*,13*Z*,24*E*-triene-1,26-dialdehyde (3). Diol **2** (400 mg, 1.06 mmol) was dissolved in CH_2Cl_2 (5 mL). This mixture was added to a stirred suspension consisting of pyridinium chlorochromate (684 mg, 3.16 mmol) and Celite (684 mg) in CH_2Cl_2 (8 mL) under nitrogen. After 2 h the starting material disappeared and the reaction mixture was diluted with Et_2O and then filtered through a pad of Florosil. This was thoroughly rinsed

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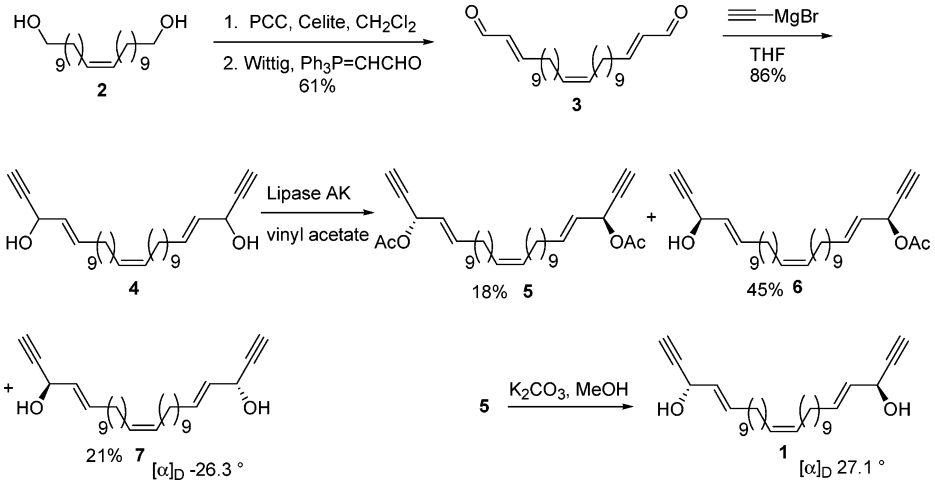
SCHEME 1



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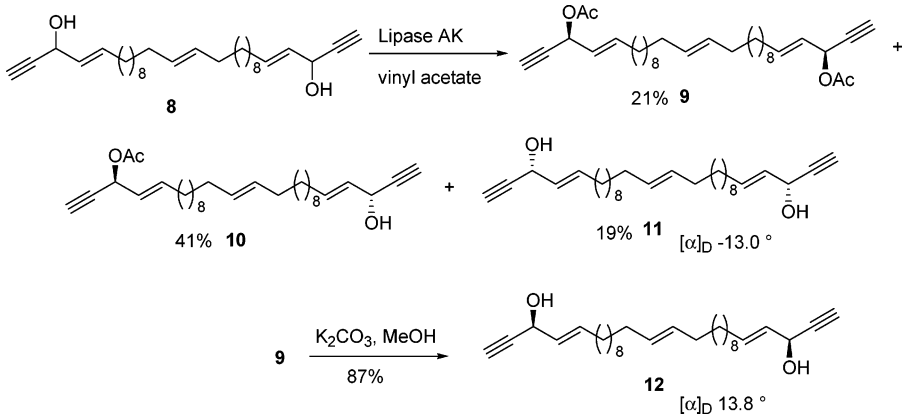

TABLE 1. Absolute Configurations of Naturally Occurring *C*2-Symmetric Acetylenic Alcohols

name	chain length	central moiety	$[\alpha]_D$	config.	origin
adociacetylene	30	furan	+21.7	S,S	*Adocia sp.*
petrosynol	30	C═C, (*Z*)	+107	S,S	*Petrocia sp.*
C20 acetylenic alcohol	20	$-CH_2CH_2$	+26	S,S	*Callyspongia pseudoreticulata*
duryne (natural)	30	C═C, (*Z*)	+29	S,S	*Cribrochalina dura*

with ether followed by removal of the solvent under reduced pressure. The crude product so obtained was subsequently dissolved in benzene (8 mL) then was treated with $Ph_3PCH{=}CHO$ (1.26 g, 4.16 mmol). The mixture was refluxed for 9 h then diluted with Et_2O. Upon completion of starting material the reaction mixture was filtered through a pad of silica. The filtrate was concentrated under reduced pressure and purified via column chromatography to afford **3** as a yellow oil (236 mg, 61%): IR 1464, 1638, 1687, 2854, 2925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2−1.5 (m, 28H), 1.93 (m, 4H), 2.27−2.33 (m, 4H), 5.36 (m, 2H), 6.09 (dd, J = 15.5, 6.9 Hz, 2H), 6.8 (dt, J = 15.6, 6.7 Hz, 2H), 9.48 (d, J = 7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 27.8, 28.6, 29.1, 29.3, 29.4, 29.6, 32.6, 32.7, 130.3, 132.9, 158.9, 194.1; HRMS calcd for $C_{26}H_{44}O_2$ (M + Na) 411.3239, found 411.3238.

Triaconta-4*E*,15*Z*,26*E*-triene-1,29-diyne-3,28-diol (4). To a solution of ethynylmagnesium bromide (2.88 mL, 1.44 mmol, 0.5 M in THF) at 0 °C under nitrogen was added, dropwise, the dialdehyde **3** (202 mg, 0.52 mmol) in THF (4 mL). The reaction progress was monitored by TLC. At the completion of the starting material the reaction mixture was quenched using saturated NH_4Cl solution and the organic layer was extracted using EtOAc. The combined organic layers were neutralized using aq $NaHCO_3$ and dried over $MgSO_4$. Purification was effected via column chromatography to afford **4** as a pale yellow solid (196 mg, 86%): mp 36−37 °C; IR 1461, 2146, 2850, 2919, 2999, 3288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.39 (m, 28 H), 1.92−2.07 (m, 8 H), 2.54 (d, J = 2.1 Hz, 2 H), 4.82 (t, J = 5.9 Hz, 2 H), 5.36 (m, 2 H), 5.59 (dd, J = 15.3, 6.5 Hz, 2 H), 5.89 (dt, J = 15.3, 6.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.15, 29.18, 29.4, 29.5, 29.6, 29.7, 31.9, 32.6, 62.8, 73.9, 83.4, 128.4, 130.4, 134.6; HRMS calcd for $C_{30}H_{48}O_2$ (M + Na) 463.3552, found 463.3547.

Enzymatic Resolution of 4. A flask was charged with lipase AK Amano '20' (360 mg), molecular sieves (360 mg), hexanes (12 mL), vinyl acetate (0.6 mL, 6.58 mmol), and the racemic diol (180 mg, 0.41 mmol). The mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC and ^1H NMR. When the amount of the diacetate was about the same as the amount of the diol, the reaction was stopped. The reaction mixture was filtered over a pad of Celite then separated by flash column chromatography to afford the diacetate **5** (65 mg, 18%), as an oil: $[\alpha]_D$ +15.3 (*c* 0.03, $CHCl_3$); IR 1461, 1739, 2125, 2854, 2925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.38 (m, 28H), 1.92−2.05 (m, 8H), 2.07 (s, 6H), 2.53 (d, J = 2.1 Hz, 2H), 5.35 (m, 2H), 5.51 (dd, J = 15.3, 6.5 Hz, 2H), 5.8 (d, J = 6.1 Hz, 2H), 5.9 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 28.6, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 32.0, 32.6, 64.1, 74.7, 80.0, 124.3, 130.3,

137.2, 169.7; MS calcd for $C_{34}H_{52}O_4$ (M + Na) 547.3, found 547.4. The monoacetate **6** (168 mg, 45%) as an oil: $[\alpha]_D$ +7.2 (*c* 0.11, $CDCl_3$); IR 1461, 1739, 2126, 2848, 2950, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.38 (m, 28H), 1.9−2.05 (m, 8H), 2.07 (s, 3H), 2.53 (d, J = 2.1 Hz, 2H), 4.82 (t, J = 5.9 Hz, 1H), 5.35 (m, 2H), 5.4−5.6 (m, 2H), 5.8 (d, J = 6.2 Hz, 1H), 5.9−6.0 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 21.1, 28.6, 28.8, 29.1, 29.2, 29.4, 29.45, 29.5, 29.53, 29.6, 31.9, 32.0, 32.6, 62.8, 64.1, 73.9, 74.7, 80.0, 83.4, 124.3, 128.4, 130.4, 130.7, 134.4, 137.2, 169.7; MS calcd for $C_{32}H_{50}O_3$ (M + Na) 505.4, found 505.4. The diol **7** (80 mg, 21%) as a solid: $[\alpha]_D$ −26.3 (*c* 0.024, $CDCl_3$); mp 41−42 °C; IR 1461, 2149, 2850, 2918, 2999, 3288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.39 (m, 28 H), 1.92−2.07 (m, 8 H), 2.54 (d, J = 2.1 Hz, 2H), 4.82 (t, J = 5.9 Hz, 2H), 5.36 (m, 2H), 5.59 (dd, J = 15.3, 6.5 Hz, 2H), 5.89 (dt, J = 15.3, 6.6, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.15, 29.18, 29.4, 29.5, 29.6, 29.7, 31.9, 32.6, 62.8, 73.9, 83.4, 128.4, 130.4, 134.6; HRMS calcd for $C_{30}H_{48}O_2$ (M + Na) 463.3552, found 463.3547.

Triaconta-4*E*,15*Z*,26*E*-triene-1,29-diyne-3*S*,28*S*-diol (1). The diacetate **5** (52 mg, 0.104 mmol) and K_2CO_3 (10 mg, 0.064 mmol) were dissolved in methanol (4 mL). The reaction mixture was stirred at rt for 2 h then quenched with diluted aq HCl and the organic layer was extracted with EtOAc. Purification was effected via column chromatography to afford **1** as a solid (42 mg, 87%): $[\alpha]_D$ +27.1 (*c* 0.017, $CHCl_3$); mp 43−45 °C; IR 1461, 2128, 2850, 2918, 2999, 3288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.39 (m, 28 H), 1.92−2.07 (m, 8 H), 2.54 (d, J = 2.1 Hz, 2 H), 4.82 (t, J = 5.9 Hz, 2H), 5.36 (m, 2H), 5.59 (dd, J = 15.3, 6.5, Hz, 2H), 5.89 (dt, J = 15.3, 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.15, 29.18, 29.4, 29.5, 29.6, 29.7, 31.9, 32.6, 62.8, 73.9, 83.4, 128.4, 130.4, 134.6; HRMS calcd for $C_{30}H_{48}O_2$ (M + Na) 463.3552, found 463.3547.

Enzymatic Resolution of 8. The same procedure described for the resolution of **4** was employed. Separation was effected via column chromatography to afford the diacetate **9** (54 mg, 21%), as an oil: $[\alpha]_D$ 9.7 (*c* 0.02, $CHCl_3$); IR 1461, 1739, 2125, 2854, 2925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.38 (m, 28H), 1.92−2.05 (m, 8H), 2.07 (s, 6H), 2.53 (d, J = 2.1 Hz, 2H), 5.35 (m, 2H), 5.51 (dd, J = 15.3, 6.5 Hz, 2H), 5.8 (d, J = 6.1 Hz, 2H), 5.9 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 28.6, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 32.0, 32.6, 64.1, 74.7, 80.0, 124.3, 130.3, 137.2, 169.7. The monoacetate **10** (94 mg, 41%) as an oil: $[\alpha]_D$ −3.9 (*c* 0.09, $CDCl_3$); IR 1461, 1739, 2126, 2848, 2950, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.38 (m, 28H), 1.9−2.05 (m, 8H), 2.07 (s, 3H), 2.53 (d, J = 2.1 Hz, 2H), 4.82 (t, J = 5.9 Hz, 1H), 5.35 (m, 2H), 5.4−5.6 (m, 2H), 5.8 (d, J = 6.2 Hz, 1H), 5.9−6.0 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 21.1, 28.6, 28.8, 29.1, 29.2, 29.4, 29.45, 29.5, 29.53, 29.6, 31.9, 32.0, 32.6, 62.8, 64.1, 73.9, 74.7, 80.0, 83.4, 124.3, 128.4, 130.4, 130.7, 134.4, 137.2, 169.7. The diol **11** (41 mg, 19%) as a solid: $[\alpha]_D$ −13 (*c* 0.07, $CDCl_3$); mp 34−35 °C; IR 1461, 2149, 2850, 2918, 2999, 3288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.39 (m, 28H), 1.92−2.07 (m, 8H), 2.54 (d, J = 2.1 Hz, 2H), 4.82 (t, J = 5.9 Hz, 2H), 5.36 (m, 2H), 5.59 (dd, J = 15.3, 6.5, Hz, 2H), 5.89 (dt, J = 15.3, 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.15, 29.18, 29.4, 29.5, 29.6, 29.7, 31.9, 32.6, 62.8, 73.9, 83.4, 128.4, 130.4, 134.6; HRMS calcd for $C_{30}H_{48}O_2$ (M + Na) 463.3552, found 463.3547.

Triaconta-4*E*,15*E*,26*E*-triene-1,29-diyne-3*S*,28*S*-diol (12). The diacetate **9** (26 mg, 0.05 mmol) and K_2CO_3 (3 mg, 0.02 mmol) were dissolved in methanol (2 mL). The reaction mixture was stirred at rt for 2 h then quenched with diluted aq HCl and the organic layer was extracted with EtOAc. Purification was effected via column chromatography to afford **12** as a solid (18 mg, 87%); $[\alpha]_D$ 13.8 (*c* 0.018, $CHCl_3$); mp 37−39 °C; IR 1461, 2128, 2850, 2918, 2999, 3288 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24−1.39 (m, 28 H), 1.92−2.07 (m, 8 H), 2.54 (d, J = 2.1 Hz, 2H), 4.82 (t, J = 5.9 Hz, 2 H), 5.36 (m, 2 H), 5.59 (dd, J = 15.3, 6.5, Hz, 2 H), 5.89 (dt, J = 15.3, 6.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.15, 29.18, 29.4, 29.5, 29.6, 29.7, 31.9, 32.6, 62.8, 73.9, 83.4, 128.4, 130.4, 134.6; HRMS calcd for $C_{30}H_{48}O_2$ (M + Na) 463.3552, found 463.3547.

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Supporting Information Available: General experimental procedures and NMR spectra for compounds **1** and **3**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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