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Synthesis of (±)-Tetrapetalone A-Me Aglycon**

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Abstract

The first synthesis of (±)-tetrapetalone A-Me aglycon is described. Key bond-forming reactions include Nazarov cyclization, a ring-closing metathesis (RCM) promoted with complete diastereoselectivity by a chiral Mo-based complex, tandem conjugate reduction-intramolecular aldol cyclization, and oxidative dearomatization.

Keywords

Cross-Coupling; Cyclization; Natural Products; Olefin Metathesis; Polycycles

Tetrapetalones (**1–4**, Figure 1) were isolated by Hirota and co-workers from *Streptomyces* sp. USF-4727, a strain of bacteria in the soil of Japan.^[1] With a core containing four fused rings including a *p*-quinol, a tetramic acid, and four contiguous stereocenters, these natural products represent a unique synthetic challenge. They also exhibit moderate inhibitory activity (IC₅₀ = 190–360 μM) against soybean lipoxygenase (SLO). Since human lipoxygenases (HLOs) are implicated in a number of inflammatory diseases,^[2] and the catalytic domain of plant and mammalian lipoxygenases is highly conserved,^[3] the study of new SLO inhibitors like tetrapetalone could lead to the identification of new HLO inhibitors.

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To aid with structural determination, Hirota and co-workers derivatized tetrapetalone A by first treating with diazomethane followed by acidic hydrolysis to furnish tetrapetalone A-Me aglycon (**5**, Figure 1).^[1c] To date, there are no reported total syntheses of the tetrapetalones, though studies toward the total synthesis of the tetrapetalones have been disclosed by the research groups of Porco,^[4] Hong,^[5] Sarpong,^[6] and Pettus.^[7]

The crucial elements of our retrosynthetic analysis of **5** are shown in Scheme 1. We projected that late-stage generation of the *para*-quinol A ring could be achieved through oxidative dearomatization of phenol **6**,^[8] and envisioned that the seven-membered C ring might be accessed by a somewhat challenging diastereoselective ring-closing metathesis (RCM) involving the sterically hindered alkenes of **7**.^[9] The requisite triene would be prepared through a cross-coupling^[10] reaction between aryl bromide **8** and an appropriately functionalized amine. Aryl bromide **8** could be formed from the Nazarov cyclization^[11] of aryl dienone **9**.

The synthesis commenced with the protection of known phenol **10**^[12] as the triisopropylsilyl (TIPS) ether and subjecting the product to Negishi coupling with methyl propiolate^[13] to furnish alkynoate **11** (Scheme 2). This material was heated with nitron **12** to generate [3+2] cycloadduct **13**, which was then oxidized to furnish aryl dienone **14** as an inseparable mixture of double-bond isomers (1.7:1) in 87% overall yield.^[14] Nazarov cyclization of this mixture using aluminium chloride^[15] produced indanone **15** as a mixture of *anti-syn* diastereomers [3.6:1 diastereomeric ratio (d.r.)]. The new carbon-carbon bond was formed exclusively at the position *para* to the triisopropylsiloxy group, in accord with Sarpong's findings.^[6] The protodesilylation of the vinyl trimethylsilane is attributed to the presence of trace amounts of Brønsted acid in the reaction mixture.^[16] This desilylation was an unexpected, but convenient means of revealing the terminal alkene needed for the anticipated RCM.

Next, **15** was subjected to a modified Krapcho decarbalkoxylation in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO)^[17] to furnish indanone **16** in 91% yield (Scheme 3). Ketone α -methylation was completely diastereoselective, occurring *anti* to the isopropenyl group on the B ring. Reduction of the ketone afforded **17** as a single diastereoisomer, indicating that hydride reduction occurs *syn* to the α -methyl group. X-ray crystallographic analysis indicated that **17** possessed the desired relative stereochemistry at C7, C8, and C9 (see Supporting Information), indicating that the hydride reduction occurs *syn* to the α -methyl group.^[6b] The secondary alcohol in **17** was protected as the *tert*-butyldimethylsilyl (TBS) ether, in preparation for Buchwald-Hartwig cross-coupling to install the C-N bond. However, under standard conditions^[10] cross-coupling attempts with various primary and secondary amines gave only trace amounts of the desired products. We attributed this to steric congestion in the vicinity of the C-Br bond, and hypothesized that a smaller coupling partner, such as NH₃, could overcome these steric issues. Indeed, aniline **18** could be prepared from **17** in an excellent yield of 97% following the protocol of Stradiotto and co-workers.^[18] The next goal was to generate a symmetric divinyl precursor analogous to **7** (Scheme 1) in order to form the C ring through an RCM reaction.

The first step toward this end was the conversion of **18** to the corresponding isocyanate, which was trapped with allylic alcohol **20** to furnish carbamate **21** (Scheme 4). This transformation was performed in preparation for an intramolecular allylic amination, which would produce a *gem*-divinyl functionality. Berkowitz and co-workers have demonstrated intramolecular allylic aminations with simple allylic carbonates,^[19] but we are not aware of examples of cyclizations executed on dienyl carbonates such as **21**. The reaction proceeded smoothly to afford divinyl oxazolidinone **22** in 71% yield, presumably *via* a π -pentadienyl palladium (II) intermediate.

Following the strategy outlined in Scheme 1, we examined a range of complexes (Figure 2) that might promote efficient and diastereoselective formation of the C ring through catalytic RCM; representative cases are illustrated in Table 1. In the presence of 25 mol % carbene **23a**,^[20] none of the ring-closed product was observed even at 80 °C after 24 h (Table 1, entry 1). It was only with a total of 90 mol% of the Ru complex, introduced over 9.0 h, that 89% conversion to a 2.4:1 mixture of **28a**:**28b** was obtained (58% yield; entry 2). Use of derivative (**23b**), which initiates metathesis faster,^[21] did not lead to improvement in efficiency or stereoselectivity (entry 3). With Mo-based bis-alkoxide **24**,^[22] only 12% conversion was observed after 25 h at ambient temperature, presumably due to relatively facile decomposition of the alkylidene (entry 4). Notably, however, the undesired diastereomer (**28b**) was generated preferentially in this experiment. Somewhat disconcertingly, the opposite sense of diastereoselectivity between Ru carbenes and dioxo-Moalkylidenes was confirmed with the finding that 12.5 mol % bis-aryloxide **25**^[23] delivered 98% conversion to a 1:3 mixture of **28a**:**28b** (90% yield, 25 h, 22 °C; entry 5).

We next probed the activity of Mo-based monoaryloxide pyrrolide (MAP) complexes.^[24] Use of complex **26a**^[25] at 22 °C afforded the desired isomer **28a** exclusively (<2% **28b**; entry 7, Table 1); at elevated temperature (40 °C), **28a** was isolated in 63% yield (63% conv.) without any detectable loss of stereoselectivity (entry 8). Further screening allowed us to determine that MAP neophylidene **26b** gives rise to a more desirable catalyst (entries 9–10); at 65 °C and in the presence of 25 mol % in situ-generated **26b**, 1.5 g of triene **22** was transformed to **28a** in 82% yield (83% conv.) and in >25:1 dr. Several additional observations regarding the diastereoselective RCM merit note: (1) Use of racemic MAP complexes suffice; enantiomerically pure alkylidenes are similarly diastereoselective, but gave little or no kinetic resolution; (2) With 10 mol % and 15 mol % **26b**, under otherwise the same conditions as illustrated in entry 10 of Table 1, 56% and 73% conversion was observed, respectively (>25:1 **28a**:**28b**); and (3) Changes in the identity of the MAP complex can engender substantial variations in efficiency and stereoselectivity, as was seen in experiments with complexes **27a–b** (entry 11–12 of Table 1). The mechanistic rationale for such selectivity fluctuations are the subject of ongoing investigations and will be disclosed in the full account of this work. (4) Although catalytic diastereoselective RCM has been previously examined and utilized in natural product synthesis,^[26] we know of no other examples in which a chiral catalyst has been used to enhance the substrate-controlled level of selectivity (i.e., from 2.4:1 to >25:1) in an olefin metathesis reaction.

The completion of the synthesis of the D ring commenced with the reduction of **28a** with an excess of LiEt_3BH ^[27] to secure amino alcohol **29** in 80% yield (Scheme 5). Alcohol **29** was then protected as the triethylsilyl (TES) ether, and chemoselective hydrogenation with Wilkinson's catalyst^[28] furnished cyclic amine **30** in 92% yield. Amine **30** was acylated with acryloyl chloride^[29] and then subjected to acid-promoted deprotection of the TES group to furnish alcohol **31** in 71% yield over two steps. Notably, alcohol **31** can be prepared on gram scale using this strategy.

To complete the assembly of the D ring, **31** was subjected to Ley oxidation^[30] to produce aldehyde **32** (Scheme 6) in 86% yield. To close the ring, we performed a tandem conjugate reduction-intramolecular aldol cyclization.^[31] Treatment of **32** with Stryker's reagent smoothly furnished tetracycle **33** as a mixture of four diastereomers in 94% combined yield.^[32] Swern oxidation^[33] of tetracycle **33** furnished chlorinated tetracycle **34** in 74% yield as a single isomer, an unexpected but precedented result.^[34] Dechlorination with zinc and acetic acid^[35] proceeded smoothly to furnish a tetramic acid which was methylated with (trimethylsilyl)diazomethane^[36] to afford tetracycle **35** in 61% yield over two steps.

Chemoselective deprotection of the phenol in tetracycle **35** was achieved with tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride,^[37] producing **36** (Scheme 7). The key oxidative dearomatization was not as straightforward as we had anticipated: treatment of phenol **36** with (diacetoxyiodo)benzene (PIDA) and [bis(trifluoroacetoxy)iodo]-benzene (PIFA)^[38] failed to give the desired *para*-quinol.^[39] Fortunately, treatment of phenol **36** with *t*BuOOH and dirhodium caprolactamate ($\text{Rh}_2(\text{Cap})_4$)^[40] generated the desired peroxide **37a** along with its C-15 epimer **37b** (1.3:1 dr) in 84% combined yield. After separation by chromatography, attempts to cleave the peroxide with Zn^0/HOAc , Mg^0/MeOH ,^[41] or Al amalgam^[42] all resulted in the regeneration of phenol **36**. These reaction conditions allowed us to recycle undesired **37b**. Ultimately, treatment of **37a** with 10% Cd/Pb couple^[43] led to successful cleavage of the peroxide to furnish *para*-quinol **38** in 76% yield. Finally, deprotection with HF-pyridine afforded ($\pm$)-tetrapetalone A-Me aglycon (($\pm$)-**5**).

The ^1H NMR spectrum obtained for ($\pm$)-**5** matches that reported by Hirota and co-workers.^[1c,44] Furthermore, a single crystal X-ray diffraction experiment unambiguously established the structure of ($\pm$)-**5** (see Supporting Info).

In summary, we have developed an effective strategy for the synthesis of tetrapetalone A-Me aglycon. Key bond-forming reactions include Nazarov cyclization to form the B ring, diastereoselective ring-closing metathesis to form the seven-membered C ring, a tandem conjugate reduction-intramolecular aldol cyclization to form the D ring, and an oxidative dearomatization to form the *para*-quinol A ring. Notably, the stereochemistry at C4, C8, C9, and C15 was relayed from the stereogenic center at C7, which was installed via Nazarov cyclization. Furthermore, the exceptional diastereoselectivity observed in the RCM reaction furnishing the C ring underscores the role that chiral catalysts can play in providing levels of efficiency as well as stereoselectivity that may not be accessible through the use of achiral complexes.^[44] Development of a strategy for the enantioselective synthesis of the tetrapetalones is underway.

Supplementary Material

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Figure 1.
Structures of tetrapetalones A–D (**1–4**) and derivative **5**.

Figure 2. Representative Ru- and Mo-based complexes examined for diastereoselective RCM of **22** to afford **28a**; Mes = 2,4,6-trimethylphenyl.

scheme 1. Retrosynthetic Analysis of **5**. RCM = ring-closing metathesis.

scheme 2.

Synthesis of bicycle **15**. a) TIPSCl, imidazole, THF, RT, 99% yield; b) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, ZnBr_2 , methyl propiolate, Et_3N , THF, 60°C , 75% yield; c) **12**, PhCH_3 , 80°C ; then *m*-CPBA, CH_2Cl_2 , 0°C , 87% yield (1.7:1 mixture of double bond isomers); d) AlCl_3 , DCE, 0°C , 79% yield (ratio of *anti*:*syn* isomers = 3.6:1). DCE = 1,2-dichloroethane, *m*-CPBA = *meta*-chloroperbenzoic acid, TIPSCl = triisopropylsilyl chloride.

scheme 3.

Synthesis of aniline **18**. a) DABCO, PhCH₃, H₂O, 80°C, 91% yield; b) LDA, CH₃I, THF, –40°C to RT; c) NaBH₄, MeOH, 0°C, 67% yield over two steps; d) TBSCl, imidazole, THF, RT, 91% yield; e) [Pd(allyl)Cl]₂, **19**, NaO^tBu, NH₃, 1,4-dioxane, PhCH₃, 110°C, 97% yield. Ad = 1-adamantyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, LDA = lithium diisopropylamine, TBSCl = *tert*-butyldimethylsilyl chloride.

scheme 4.

Synthesis of tetracycle **22**. a) $\text{C}(\text{O})\text{Cl}_2$, PhCH_3 , aq. NaHCO_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$; then **20**, DMAP, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 69% yield; b) $\text{Pd}(\text{PPh}_3)_4$, THF, $40\text{ }^\circ\text{C}$, 71% yield; DMAP = 4-N,N-dimethylaminopyridine.

scheme 5.

Synthesis of alcohol **31**. a) LiEt_3BH , THF, 0°C , 80% yield; b) TESCl , imidazole, DMF, 40°C , 88% yield; c) $(\text{PPh}_3)_3\text{RhCl}$, 1 atm H_2 , PhCH_3 , 92% yield; d) acryloyl chloride, DIEPA, 4Å MS, PhCH_3 , 50°C ; e) HCl , H_2O , MeOH , THF, RT, 71% over two steps. DIEPA = N,N-diisopropylethylamine, DMF = N,N-dimethylformamide, MS = Molecular Sieves, TES = triethylsilyl.

scheme 6.

Synthesis of tetracycle **35**. a) TPAP, NMO, 4 Å MS, CH₂Cl₂, CH₃CN, 0°C, 86% yield; b) [PPh₃CuH]₆, PhCH₃, 0°C, 94% yield; c) DMSO, (COCl)₂, Et₃N, CH₂Cl₂, -78°C to RT, 74% yield; d) Zn, HOAc, CH₂Cl₂, RT; e) (TMS)CHN₂, MeOH, CHCl₃, RT, 61% yield over two steps. DMSO = dimethyl sulfoxide, MS = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate, TMS = trimethylsilyl.

scheme 7.

Synthesis of (±)-5. a) TBAF(*t*BuOH)₄, THF, RT, quant. yield; b) Rh₂(Cap)₄, *t*BuOOH, DCE, 78 °C, 1.3:1 *dr*, 84% yield; c) 10% Cd/Pb couple, THF, 1M aq. NH₄OAc, RT, 76% yield; d) HF-pyridine, THF, RT, 61% yield. TBAF = tetrabutylammonium fluoride, Cap = caprolactamate, DCE = 1,2-dichloroethane.

Table 1

Examination of Ru- and Mo-based complexes for diastereoselective conversion of triene **22** to tetracyclic dienes **28a/28b**.^[a]

Entry	Catalyst; mol %	T [°C]; t [h]	Conv. [%]; ^[b] Yield [%]; ^[c]	Ratio 28a:28b ^[b]
1	23a ; 25	80; 24	<2	–
2	23a ; 90 ^[d]	85; 9	89 ^[f] ; 58	2.4:1
3	23b ; 75 ^[e]	80; 36	77 ^[f] ; 56	2.4:1
4	24 ; 25	22; 25	12; nd	1:5
5	25 ; 12.5	22; 25	98; 90	1:3
7	26a ; 25	22; 25	50; nd	>25:1
8	26a ; 25	40; 25	63; 63	>25:1
9	26b ; 25	25; 25	58; nd	>25:1
10	26b ; 25	65; 20	83 ^[f] ; 82	>25:1
11	27a ; 25	22; 25	28; nd	>25:1
12	27b ; 25	22; 25	49; 40	1:1

^[a] Reactions were performed under N₂ in toluene (0.015M – 0.05M for entries 1–3) or benzene (0.1 – 0.13M for entries 4–11).

^[b] Determined by analysis of the 400 MHz ¹H NMR spectra of the unpurified mixtures.

^[c] Yield of isolated and purified products.

^[d] Initial loading was 5 mol % with an additional 5 mol % introduced every 30 min.

^[e] Initial loading was 25 mol % and an additional 25 mol % was introduced every 12 h.

^[f] Determined by isolation and purification of products and unreacted starting materials

nd = not determined.