Pergamon

Tetrahedron Letters 43 (2002) 4107–4110

TETRAHEDRON LETTERS

Synthetic studies toward cyathin diterpenoids: approach to the tricyclic system through intramolecular Heck-type cyclization

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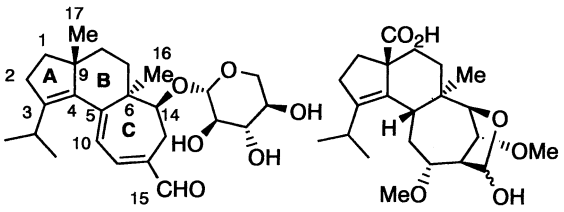
Accepted 21 March 2002

Abstract—The enantioselective synthesis of a model of the core ring system of cyathin diterpenes is described. The key tricyclic acetate **4** was assembled via an intramolecular Heck-type cyclization of the chiral triflate **8**. Acetate **4** was taken through to model cyathan ketones **3a** and **3b** by a one-carbon ring expansion.

Stimulators of nerve growth factor (NGF) synthesis have been expected as medicine for degenerative neuronal disorders such as Alzheimer's disease and peripheral nerve regeneration.[1] Recently two classes of related diterpenoid natural products isolated from fungi, the erinacines[2] and scabronines[3] have been shown to have significant NGF synthesis stimulating activity (Fig. 1).

The structural novelty and the biological activity displayed by the cyathins have drawn much attention to their synthesis. However, to date no enantioselective synthesis of cyathins has been accomplished.[4] The central synthetic challenge in the design of a route to cyathins is the control of the *anti* relative stereochemistry between the rings A and C. In this letter, we wish to describe a sound solution to this problem, involving the enantioselective synthesis of the tricyclic acetate **4** by Heck-type cyclization of triflate **8**, and further elaboration of **4** into ketones **3a**,**b**, which display the correct stereochemistry of the cyathin family. Intramolecular Heck reactions using prochiral dienes tethered to vinylic halide or triflate moieties, are powerful tools for the rapid construction of polycyclic compounds.[5] Thus, we first planned to elaborate a model of the cyathane-ring system by palladium-catalyzed cyclization of the triflate **9** possessing a cycloheptadiene moiety. However, we faced a number of difficulties to prepare the required ester **7**, and we also failed to alkylate efficiently other seven-membered ring derivatives (such as 2-methyl-1,3-cycloheptanedione or 2-methyl-cycloheptenone) with the iodo derivative **5**. An alternative plan was therefore designed, targeting a C-*nor*-cyathane derivative such as the acetate **4**. The seven-membered C-ring would ultimately be derived through a one-carbon ring enlargement reaction.[6] Accordingly, the crucial coupling of the chiral A-ring synthon with the C-ring subunit would simply be performed by alkylation of the enolate of the cyclohexadiene ester **6** with iodide **5** (Scheme 1).



Erinacine A: **1** Scabronine A: **2**

Figure 1.

The chiral synthon **5** was prepared from the known keto ester (*R*)-**10**, which is easily accessible with a high enantiomeric purity via the deracemizing Michael addition reaction involving the chiral imine derived from 1-methylcyclopentanone and (*S*)-1-phenylethylamine.[7] Temporary shielding of the keto group was first undertaken. To this aim, **10** was reduced with sodium borohydride, and the mixture of epimeric alcohols obtained was protected as *t*-butyldimethysilyl ethers. Saponification of the ester group of **11** delivered the corresponding acid **12** in 72% overall yield from **10**. Iododecarboxylation of the propionic side chain was

Keywords: terpene; Heck reactions; ring transformation; dienes; diastereoselection.

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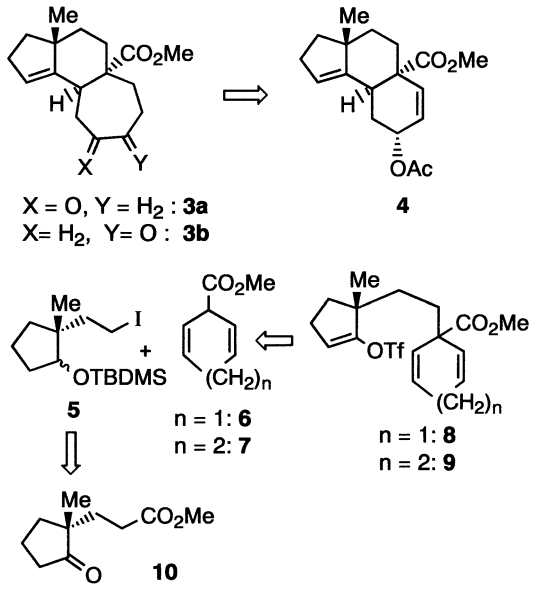
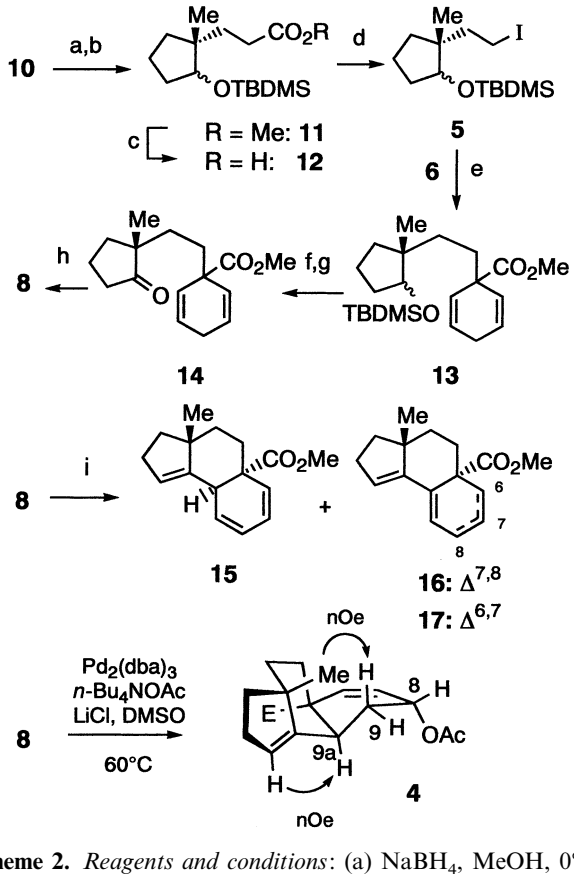
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00570-1



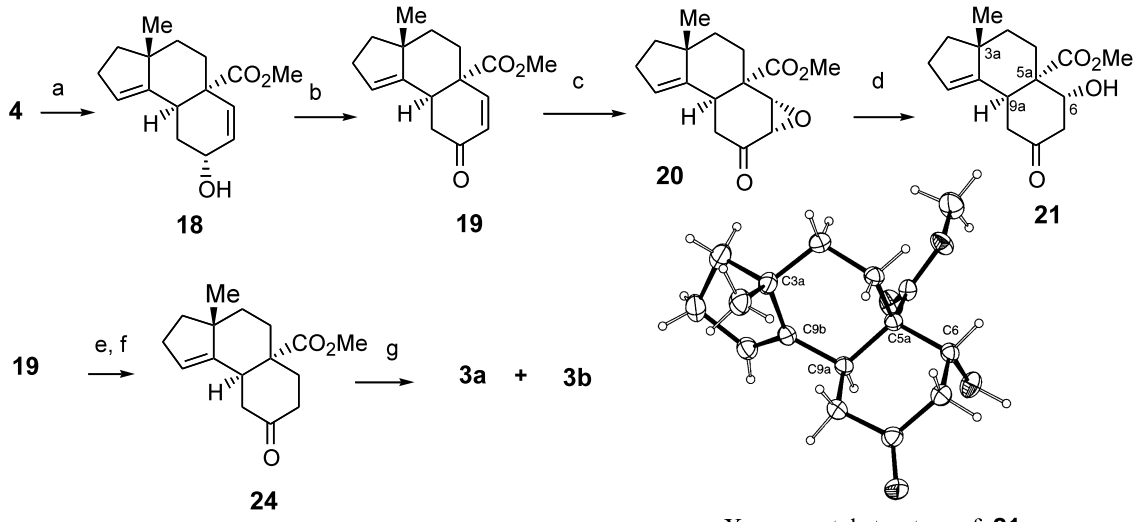
Scheme 1.

then achieved by treatment of acid **12** with $Pb(OAc)_4/I_2$ according to the Barton[8] modification of the Kochi reaction to provide **5** in 80% yield. The coupling between the lithium enolate of the ester **6**[9] and the iodo derivative **5** turned out to be quite difficult, and required heating in the presence of DMPU. In such conditions the diene ester **13** was obtained in 83% yield. Removal of the *tert*-butyldimethylsilyl group with tetra-*n*-butylammonium fluoride in refluxing THF, followed by Swern oxidation led to the ketone **14**, which was taken through enol triflate **8** by using triflic anhydride in the presence of 2,6-di-*tert*-butylpyridine.[10] At this stage, we stood ready to check the crucial palladium-catalyzed cyclization. In the event, treatment of triflate **8** in standard Heck conditions ($Pd(OAc)_2$ cat., K_2CO_3) was disappointing, giving rise to a mixture of trienes **15**, **16** and **17** in low yield (<15%), along with a minute amount of allylic acetate **4** (<10%). Since the latter product was formed by addition of acetate ions from $Pd(OAc)_2$ on the intermediate η^3 palladium complex, the influence of acetate ions was studied with the hope to drive the reaction course toward the desired acetate **4**.[11] Gratifyingly, treatment of triflate **8** with Pd_2dba_3 as catalyst (5%) in the presence of 3 equiv. of tetrabutylammonium acetate in DMSO at 60°C provided tricyclic acetate **4** in 85% yield. The stereochemical assignment of **4** was inferred from ^1H NMR spectroscopy including NOESY experiments. The pseudo-axial configuration of the methine hydrogen at C-9a ($\delta = 3.43$) in respect to the C-ring, was deduced from the coupling constants ($J = 14.5$ and 3.5 Hz) with vicinal H-9α and H-9β protons, respectively. Furthermore, a strong correlation between the H-10β proton and the angular methyl group in the NOESY chart are consistent only with the *anti-cis* configuration of **4**. This assignment was subsequently confirmed by X-ray crystallography (vide infra). Interestingly, while the formation of the *cis* BC-ring junction could be anticipated in view of the known steric course of such intramolecular Heck reaction;[5] however, the influence of the quaternary stereogenic center to direct the reaction onto the face opposite to the methyl group seemed unprecedented. This high stereoselectivity in the ring-closure reaction could be related to steric interactions and/or the introduction of conformational strain in the tether, which does not favor a transition state that leads to the angular substituents being on the same side of the molecule. Thus, the tandem Heck reaction–acetate ion capture process[11] appears to be a viable method to establish the crucial *anti* relationship of A and C rings of the cyathane skeleton (Scheme 2).

The remaining task was the one-carbon expansion of the C-ring. We first planned to introduce the C-14 hydroxyl group before implementing the ring enlargement. Thus, acetate **4** was treated with sodium methoxide in methanol, and the resulting allylic alcohol **18**[12] oxidized with MnO_2 affording a 73% yield of **19**. Base-catalyzed epoxidation occurred exclusively by the convex face, delivering keto-epoxide **20** in 90% yield. Treatment of the latter with sodium (phenylseleno)trimethoxy borate[13] next provided the hydroxy ketone **21** (75% isolated yield). The stereochemistry of



Scheme 2. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0°C, 91%; (b) TBDMSCl, Im, DMF, 20°C, 12 h, 90%; (c) aq. KOH, MeOH, 20°C, 89%; (d) $Pb(OAc)_4/I_2$, *hv*, refluxing CCl_4; (e) i. **6**, LDA, THF, −78°C, 1 h, ii. DMPU, THF, 50°C, 3 h, 83%; (f) *n*-Bu_4NF, THF, 60°C, 5 h, 78%; (g) $(ClCO)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, 95%; (h) 2,6-di-*tert*-buylpyridine, Tf_2O, CH_2Cl_2, 0°C, 79%; (i) $PdOAc_2$ cat., K_2CO_3, *n*-Bu_4NBr, DMA, 100°C, 8 h.



X-ray crystal structure of **21**

Scheme 3. *Reagents and conditions*: (a) MeONa, MeOH, 20°C, 3 h, 96%; (b) MnO_2, toluene, 80°C, 3 h, 73%; (c) H_2O_2, NaOH, MeOH, 20°C, 12 h, 90%; (d) PhSeSePh, $NaBH_4$, MeOH, AcOH cat. 0°C, 3 h, 75%; (e) Li, NH_3, *t*-BuOH–THF, −78°C; (f) PCC, CH_2Cl_2, AcONa, 4 Å sieves, 20°C, 78%; (g) i. $TMSCHN_2$, $AlMe_3$, −78 to 20°C, 3 h, ii: TFA, THF, H_2O, 78%.

the four stereocenters in **21** was assigned by X-ray diffraction analysis.[14] This analysis confirmed the *anti* relationship between the two angular substituents, as previously established by NMR. At this point, inversion and protection of the C-6 hydroxyl group were required. Unfortunately, numerous attempts to address this issue failed due to an extremely easy β-elimination reaction of **21** reverting to enone **19**, either under conventional protection conditions, or employing Mitsunobu protocol. Given the potential difficulties to perform the ring expansion reaction with **21**, we decided to evaluate the process with model ketone **24**. Accordingly, enone **19** was reduced with lithium in liquid ammonia, and the crude alcohol obtained was oxidized with PCC to give ketone **24**. Treatment of this material with (trimethylsilyl)diazomethane in presence of Me_3Al[15] provided after acidic work-up a 1.5:1 mixture of ketone **3a** and **3b** with a combined 78% yield (Scheme 3). Since a higher selectivity could be expected for more substituted compounds, this work constitutes a useful stereocontrolled route for the construction of the ABC rings of cyathins. Studies are now in progress toward syntheses of erinacine A and other cyathin derivatives, according to the present strategy.

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12. Compound **18**: Colorless oil; $[\alpha]_D$ −4.4 (EtOH, $c=2$); IR (neat, cm^{-1}) 3600–3100, 1728, 1640, 1460, 1430; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.92 (ddd, $J=9.9$, 5.5, 1.4 Hz, 1H), 5.76 (d, $J=9.9$ Hz, 1H), 5.46 (m, 1H), 4.11 (ddd, $J=5.5$, 3.9, 2.0 Hz, 1H), 3.65 (s, 3H), 3.44 (dd, $J=14.2$, 2.8 Hz, 1H); 2.35–2.25 (m, 1H), 2.15 (dddd, $J=15.9$, 9.1, 3.1, 1.3 Hz, 1H), 2.08–2.01 (m, 1H), 2.00 (broad s, 1H), 1.92 (dt, $J=3.9$, 14.2 Hz, 1H), 1.76–1.52 (m, 5H); 1.21 (dt, $J=$ 14.2, 3.5 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 175.1 (C), 149.4 (C), 134.7 (CH), 128.1 (CH), 124.1 (CH), 63.1 (CH), 52.2 (CH_3), 50.7 (C), 44.5 (C), 43.2 (CH_2), 37.9 (CH_2), 35.5 (CH_2), 32.5 (CH), 29.1 (CH_2), 27.5 (CH_2), 25.1 (CH_3); Anal. calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.27; H, 8.61.
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14. Compound **21**: Colorless crystal, mp 168–170°C; IR (neat, cm^{-1}) ν 3500–3300, 1731, 1702; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.49 (s, 1H), 4.36 (t, $J=3.4$ Hz, 1H), 3.71 (m, 4H), 2.78 (dd, $J=14.8$, 3.1 Hz, 1H), 2.58 (dd, $J=15.1$, 13.1 Hz, 1H), 2.47 (ddd, $J=14.8$, 3.7, 2.4 Hz, 1H), 2.35 (ddd, $J=15.1$, 5.8, 2.3 Hz, 1H), 2.31 (m, 1H), 2.17 (ddd, $J=16.1$, 9.1, 3.1 Hz, 1H), 2.05–1.95 (m, 2H), 1.81 (dt, $J=13.9$, 3.4 Hz, 1H), 1.75 (dd, $J=12.1$, 7.0 Hz, 1H), 1.60 (t, $J=12.1$ Hz, 1H), 1.26 (m, 1H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.5 (C), 174.5 (C), 147.1 (C), 125.6 (CH), 75.5 (CH), 53.1 (C), 52.1 (CH_3), 45.0 (C), 44.1 (CH_2), 44.0 (CH_2), 42.5 (C), 37.9 (CH_2), 37.2 (CH), 29.1 (CH_2), 26.0 (CH_3), 25.4 (CH_2). Crystallographic data: crystal of 0.100×0.275×0.375 mm, $C_{16}H_{22}O_4$, $M_w=278.34$, orthorhombic system, space group $P2_12_12_1$, $Z=4$, $a=8.902(3)$, $b=12.533(3)$, $c=12.918(4)$ Å, $V=1441.2$ Å^3, $d_{calcd}=1.283$ g cm^{-3}, $F(000)=600$, λ (Mo Kα) $=0.71073$ Å, $\mu=0.091$ mm^{-1}. 5609 data were measured with a Nonius Kappa-CCD diffractometer. The structure was refined with program SHELXL-93. Refinement of 187 parameters converged to $R1(F)=0.0325$ for the 1631 observed reflections having $I\geq 2\sigma(I)$, and $wR_2(F^2)=0.0741$ for all the 1787 unique data, with a goodness-of-fit S factor of 1.073. The residual electron density was found between –0.11 and 0.10 e Å^{-3}. Crystallographic results have been deposited (CIF file) with the Cambridge Crystallographic Data Centre, UK, and allocated the deposition number CCDC 179328.

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