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Asymmetric synthesis of the tricyclic core of cyathin diterpenoids via intramolecular Heck reaction

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Abstract—The enantioselective synthesis of the ketones **3** which displays the carbon core of NGF-inducing cyathane diterpenes is described. The key tricyclic trienone **22** was assembled in 13 steps from Michael adduct (*R*)-**8a** via intramolecular Heck cyclization of the chiral triflate **21**. The trienone **22** was further elaborated into ketone **3** through trimethylaluminum-promoted expansion of the C-ring with trimethylsilyldiazomethane.

Cyathane diterpenes exemplified by erinacine A **1** are of significant medicinal interest because they are potent stimulators of nerve growth factor (NGF) synthesis.[1] NGF is a potential treatment for degenerative neural disorders such as Alzheimer's disease and for promoting peripheral nerve regeneration.[2] However, NGF's inability to cross the blood–brain barriers limits its utility, hence drugs that stimulate NGF synthesis by brain cells show great promise as new medicines. Considering the therapeutic potential of the erinacines, combined with their scarce availability from natural sources, a general synthetic route to these molecules and derivatives would be of great interest. As a result, the cyathins diterpenoids have drawn much attention from the synthetic community.[3] We recently described an enantioselective synthetic route to keto esters **2** in which the crucial control of the *anti*-relative stereochemistry between the rings A and C is achieved by means of an intramolecular Heck-type cyclization.[4]

The starting material in this approach was the keto ester (*R*)-**8a**, which is easily accessible in high optical purity via the deracemizing Michael addition involving the chiral imine derived from 2-methylcyclopentanone and (*S*)-1-phenylethylamine.[5]

Herein, we disclose an extension of our earlier work allowing the implementation of the requisite isopropyl group at C-3 and suitable functionalities in the seven-membered C-ring, culminating in the synthesis of ketone **3**. Our initial plan was to set the isopropyl group at the outset of the synthetic scheme using keto ester (*R*)-**8a** as the starting material. We assumed that the keto ester **8b** so obtained could be further elaborated into alkenyl triflate **6**, which in turn can undergo Heck cyclization to give the C-*nor*-cyathane derivative **4**. Finally, a regioselective one-carbon ring expansion reaction should complete the synthesis (Scheme 1).

The requisite keto ester **8b** was synthetized in five steps and 47% overall yield from (*R*)-**8a** (ee = 91%).[5a] Thus, reaction of **8a** with TMSOTf led to the expected silylated enol ether **9**. Mukaiyama condensation with acetaldehyde, followed by sequential mesylate formation and β-elimination with DBU produced enone **11** as a 5:1 *E*/*Z* mixture in 75% overall yield from **8a**. This compound was converted into the desired keto ester **8b** (as a 1:1 diastereomeric mixture at C-5) upon treatment with lithium dimethylcuprate.

The next task was to further functionalize compound **8b** to allow the connection with the C-ring synthon **5**.[6] Our initial plan involved activation of the keto group into triflate enol ester and iododecarboxylation of the propanoic side chain. Unfortunately, formation of the enol triflate from the highly hindered keto group of **8b** required drastic conditions and furnished the

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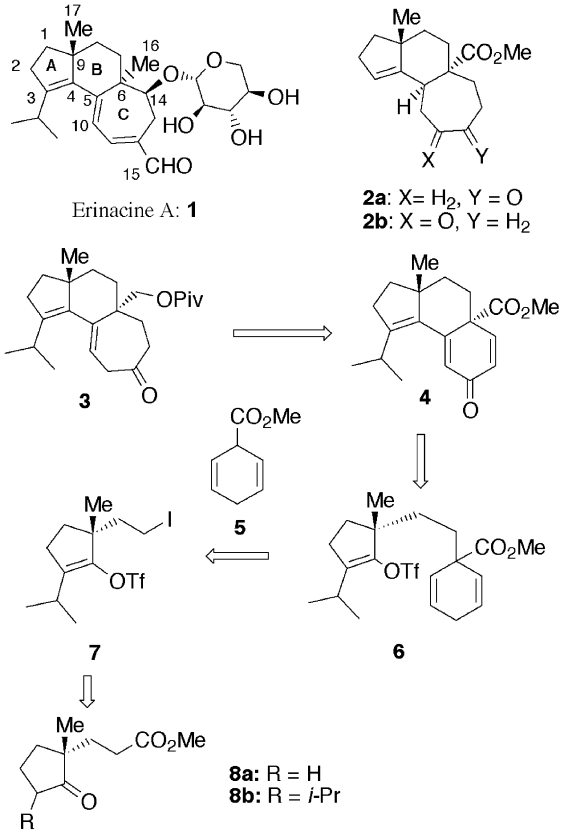
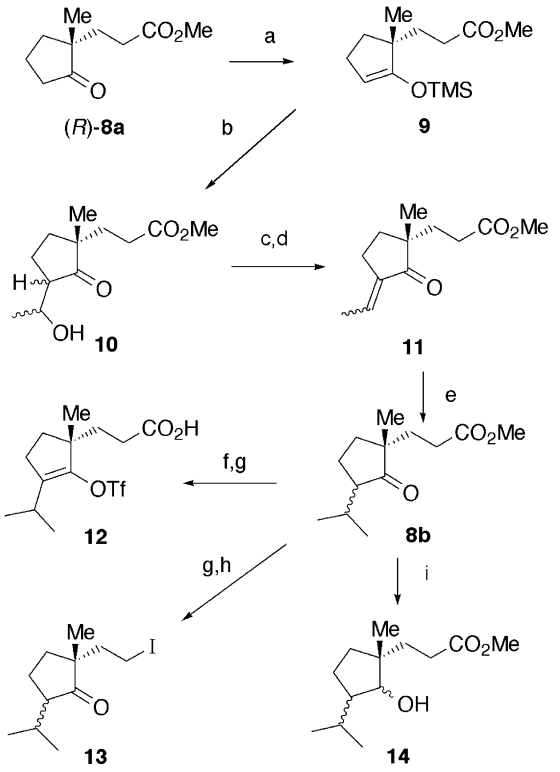


Scheme 1.



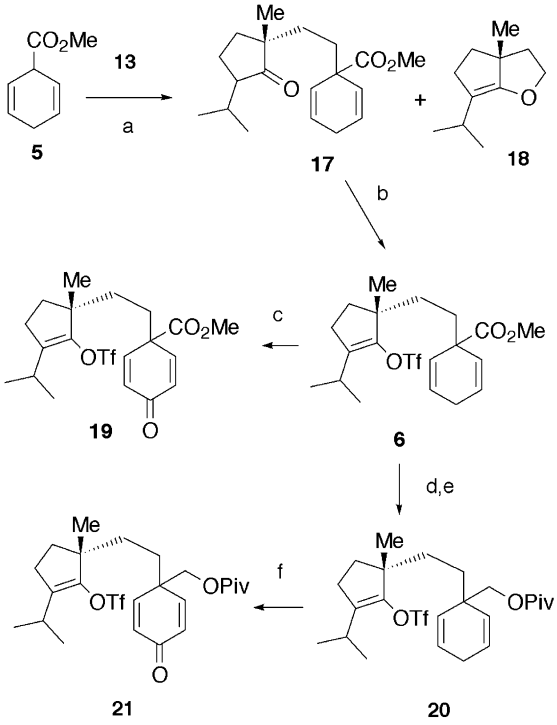
Scheme 2. Reagents and conditions: (a) 1.1 equiv TMSOTf, E_3N, CH_2Cl_2, 4 h, 20 °C, 89%; (b) $TiCl_4$, CH_3CHO, −78 °C, 2 h, 89%; (c) MsCl, Et_3N, DMAP, 0 °C, 3 h, 95%; (d) DBU, toluene, 110 °C, 1.5 h, 90%; (e) Me_2CuLi, Et_2O, −78 °C, 2 h, 70%; (f) Tf_2O, 2,6-(*t*-Bu)$_2C_5H_3N$, $C_2H_4Cl_2$, 80 °C, 10 h, 30%; (g) KOH, H_2O, MeOH, 20 °C, 12 h, 80%; (h) $Pb(OAc)_4$, I_2, visible light, CCl_4, 80 °C, 1.5 h, 65%; (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 3 h, 45%.

corresponding triflate in low yield. Furthermore, after saponification of the ester group, the Barton modification of the Kochi reaction[7] ($Pb(OAc)_4/I_2$, refluxing CCl_4) failed to give the desired iodo triflate **7**. On the other hand, saponification of **8b** followed by Kochi reaction produced the iodo ketone **13** in 52% overall yield. Unfortunately, this sensitive material was found to decompose upon treatment with Tf_2O.

Consequently, we postponed the formation of the triflate enol ether to a latter stage of the synthesis and decided to explore the temporary shielding of the keto group of **8b**. Since we have previously shown that protection of the ketone with a dioxolane group impeded the coupling with cyclohexadiene ester **5**,[4] we turned to a reduction–protection sequence. However, new problems stemmed from the steric hindrance around the ketonic carbonyl group. Most usual reducing reagents such as $NaBH_4$ or $NaBH_4$-$CeCl_3$ reacted very sluggishly with **8b**, giving a mixture of alcohols **14**, along the corresponding lactones and over-reduction diols. Therefore, this cumbersome route was not pursued further (Scheme 2).

After considerable experimentation, it was finally found that the alkylation of the lithium enolate of cyclohexadiene ester **5** with iodo ketone **13**, provided the desired keto ester **17** in 60% yield along with a small amount of the volatile ether **18**. Remarkably, the presence of the *unprotected keto group* in **13** was not prejudicial to the efficiency of the alkylation step. Having secured the critical union of subunits A and C, we turned our attention to the closing of the tricyclic ring system through the Heck reaction-anion capture process we previously described.[4,8] Preparation of the alkenyl triflate (*S*)-**6** occurred smoothly by treatment of **17** with triflic anhydride in refluxing 1,2-dichloroethane. However, the presence of the isopropyl group deeply affected the reactivity of triflate **6** in Heck reactions. For example, treatment of **6** with $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of an acetate ion source as previously reported[4] let the starting material unchanged. All attempts at improving this result using various palladium catalysts and reaction conditions failed. We felt that the lack of reactivity of **6** might be overcome by adding a carbonyl group at the C-4 position of the cyclohexadienyl appendage.[9]

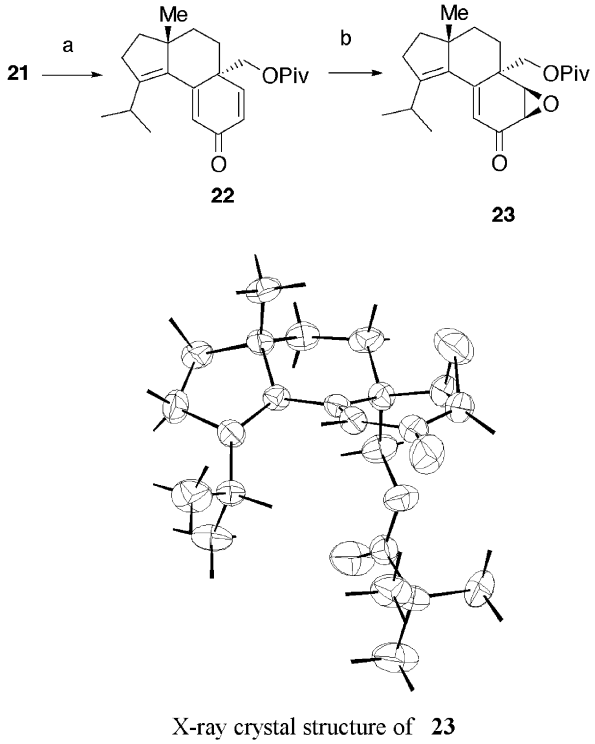
Allylic oxidation of (*S*)-**6** with $CrO_3{\cdot}$3,5-DMP[10] gave the expected dienone (*S*)-**19**, albeit in very low yield. Instead, products with an aromatic C-ring whose structures were not readily formulated were produced. By contrast, allylic oxidation of the pivalate **20** (obtained in 72% yield upon treatment of **6** with DIBAL-H, followed by esterification with *t*-BuCOCl) provided the desired dienone (*S*)-**21** in 60% yield (Scheme 3). Treatment of alkenyl triflate **21** with $Pd(OAc)_2/PPh_3$/*n*-Bu_4NBr in toluene at 120 °C proceeded smoothly affording trienone (+)-**22** (70% isolated yield) with high diastereoselectivity (95:5).[11] The *anti*-relative configura-



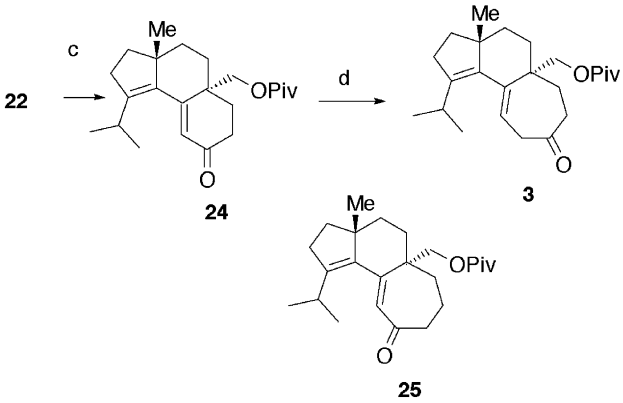
Scheme 3. Reagents and conditions: (a) (i): LDA, THF, −78 °C, 40 min, (ii): HMPA, **13**, 1.5 h, 50 °C, 60%; (b) Tf_2O, 2,6-(*t*-Bu)$_2$-C_5H_3N, $C_2H_4Cl_2$, 80 °C, 8 h, 65%; (c) CrO_3·3,5-DMP, CH_2Cl_2, 6 h, 20 °C, 20%; (d) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, then 2 h, 0 °C, 80%; (e) *t*-BuCOCl, py, DMAP, CH_2Cl_2, 15 h, 20 °C, 90%; (f) CrO_3, 3,5-DMP, CH_2Cl_2, 6 h, 20 °C, 60%.

tion between rings A and C of the main isomer was unambiguously established by X-ray crystallography analysis of the epoxide **23**[12] derived from **22** by base catalyzed epoxidation reaction. Interestingly, in this process, attack of the hydroperoxide anion occurred mainly (5:1) on the less hindered face of the molecule, namely on the face opposite to the bulky pivalate group.[13] The remaining task was the one-carbon expansion of the C-ring of trienone **22**. However, this densely functionalized material was found to have a tendency to give aromatic decomposition products with a variety of reagents, presumably through cleavage of the pivalate group followed by retro-aldol type process. To overcome that trend, we decided to reduce the less hindered double bond of **22**. Thus, homogeneous hydrogenation of the trienone **22** using Wilkinson catalyst furnished the desired dienone **24** in 75% yield.

At this stage, it was felt that aluminum catalyzed carbenoid insertion was the most expeditious way to address the challenge of regioselective expansion of the dienone **24** to the cyathane core. Thus, when the latter compound was treated with trimethylsilyldiazomethane in the presence of trimethylaluminum[14] followed by hydrolysis of the resulting enol ether, the expanded ketone (+)-**3** was obtained in 60% isolated yield along with 15% of the regioisomeric enone **25** (Scheme 4).[15] To our knowledge, the preferential migration of the unsaturated α-side of enones in such a process is unprecedented, although a similar trend was previously observed with 1-tetralone derivatives.[16]



X-ray crystal structure of **23**



Scheme 4. Reagents and conditions: (a) 7 mol % $Pd(OAc)_2$, 15 mol % PPh_3, K_2CO_3, *n*-Bu_4NBr, toluene, 2 h, 120 °C, 70%; (b) NaOH 5%, H_2O_2, MeOH, 25 °C, 24 h, 50%; (c) $(PPh_3)_3RhCl$, H_2, EtOH, 25 °C, 36 h, 75%; (d) (i): $TMSCHN_2$, $AlMe_3$, THF, −78 °C, then 36 h, 30 °C, (ii): HCl 3 N, acetone 2 h, 60%.

In summary, we have successfully assembled the tricyclic carbon core of the cyathins in optically active form in 18 steps from 2-methylcyclopentanone. The key steps of our synthesis were the enantioselective Michael addition to settle the absolute configuration, intramolecular Heck reaction to establish the crucial anti-stereochemistry of the C-*nor*-cyathane **22**, and the organoaluminum-promoted diazoalkane mediated ring expansion of the C-ring. Further elaboration of ketone (+)-**3** into erinacine A and other cyathane diterpenes, requires the reduction of the angular hydroxymethyl group into a methyl group, manipulation of the C-12 carbonyl to introduce the requisite carbaldehyde and functionalization at C-14. Epoxide **23**, which displays an oxygen atom with the correct β-configuration at the future C-14 center might serve as a suitable starting material for this purpose.

Acknowledgements

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References and notes

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11. Compound **22**: Colorless oil; $[\alpha]_D$ +82.5 (EtOH, $c = 2$); IR (neat, cm^{-1}) 1734, 1658, 1624, 1450, 1239, 1209; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.79 (d, $J = 10.0$ Hz, 1H), 6.34 (dd, $J = 10.0$, 1.3 Hz, 1H), 6.18 (d, $J = 1.3$ Hz, 1H), 4.27 (d, $J = 10.5$ Hz, 1H), 4.05 (d, $J = 10.5$ Hz, 1H), 2.85 (hept, $J = 6.8$ Hz, 1H), 2.50–2.40 (m, 2H), 1.94 (dt, $J = 12.8$, 2.7 Hz, 1H), 1.88 (ddd, $J = 12.6$, 6.8, 2.7 Hz, 1H), 1.84–1.67 (m, 4H), 1.11 (s, 9H), 1.05 (d, $J = 6.8$, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.9 (C), 177.9 (C), 157.5 (C), 152.1 (CH), 147.1 (C), 136.5 (C), 129.7 (CH), 127.6 (CH), 66.2 (CH_2), 49.9 (C), 45.3 (C), 39.7 (C), 39.6 (CH_2), 36.1 (CH_2), 31.8 (CH_2), 29.0 (CH_2), 27.1 (CH), 26.9 ($3CH_3$), 23.5 (CH_3), 21.5 (CH_3), 21.4 (CH_3).
12. Compound **23**: Colorless crystals; mp 159 °C (*i*-Pr_2O); IR (neat, cm^{-1}) 1727, 1668, 1461, 1410, 1280; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.86 (s, 1H), 4.22 (d, $J = 11.2$ Hz, 1H), 4.06 (d, $J = 11.2$ Hz, 1H), 3.50–3.45 (m, 2H), 2.76 (hept, $J = 6.8$ Hz, 1H), 2.45–2.40 (m, 2H), 2.29 (td, $J = 13.8$, 4.8 Hz, 1H), 1.91 (dt, $J = 12.8$, 2.7 Hz, 1H), 1.86–1.60 (m, 4H), 1.13 (s, 9H), 1.03 (d, $J = 6.8$, 3H), 1.02 (s, 3H), 0.92 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.0 (C), 181.0 (C), 163.0 (C), 159.6 (C), 145.2 (C), 124.0 (CH), 66.8 (CH_2), 60.7 (CH), 55.3 (CH), 47.9 (C), 46.0 (C), 39.0 (CH_2), 38.9 (C), 36.1 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 27.0 ($3CH_3$), 26.7 (CH), 23.5 (CH_3), 21.5 ($2CH_3$); Crystallographic data: crystal of $0.23 \times 0.25 \times 0.29$ mm. $C_{23}H_{32}O_4$, $M = 372.50$: orthorhombic, space group P 21 21 21 (No. 19), $Z = 4$, $a = 10.511(5)$, $b = 12.617(5)$, $c = 15.818(5)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2097.9(15)$ $Å^3$, $d = 1.179$ g cm^{-3}, $F(000) = 808$, $\lambda = 0.710693$ Å(Mo Kα), $\mu = 0.079$ mm^{-1}; 5788 reflections measured ($0 \leqslant h \leqslant 14$, $0 \leqslant k \leqslant 17$, $0 \leqslant l \leqslant 22$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92 and refined with CRYSTALS. Hydrogen atoms riding. Refinement converged to $R(gt) = 0.0493$ for the 1716 reflections having $I \geqslant 2\sigma(I)$, and $wR(gt) = 0.1041$, goodness-of-fit $S = 0.9117$. Residual electron density: −0.25 and 0.29 $eÅ^3$. Crystallographic results have been deposited (CIF file), in the Cambridge Crystallographic Data Centre, UK, and allocated the deposition number CCDC 267231.
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15. Compound **3**: $[\alpha]_D$ +285 (EtOH, $c = 0.8$); IR (neat, cm^{-1}) 2957, 2934, 2865, 1727, 1667, 1479, 1458, 1150; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.30 (t, $J = 6.5$ Hz, 1H), 3.97 (d, $J = 11.2$ Hz, 1H), 3.93 (d, $J = 11.2$ Hz, 1H), 3.18 (dd, $J = 14.4$ Hz, $J = 6.2$ Hz, 1H), 3.48 (dd, $J = 14.4$ Hz, $J = 6.7$ Hz, 1H), 2.71 (hept, $J = 6.8$ Hz, 1H), 2.72–2.60 (m, 1H), 2.52 (ddd, $J = 18.8$ Hz, $J = 8.9$ Hz, $J = 2.3$ Hz, 1H), 2.35–2.25 (m, 3H), 1.95–1.50 (m, 6H), 1.38 (dt, $J = 13.8$ Hz, $J = 3.3$ Hz, 1H), 1.79 (s, 9H), 0.94 (d, $J = 6.8$, 3H), 0.92 (s, 3H), 0.90 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.2 (C), 178.2 (C), 142.3 (C), 139.9 (C), 139.7 (C), 117.8 (CH), 66.8 (CH_2), 48.7 (C), 44.8 (C), 41.6 (CH_2), 38.9 (C), 38.7 (CH_2), 37.8 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 30.7 (CH_2), 28.3 (CH_2), 27.3 ($3CH_3$), 26.4 (CH), 23.4 (CH_3), 21.6 (CH_3), 21.3 (CH_3); Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; Found: C, 77.15; H, 9.84.
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