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Enantioselective synthesis of the tricyclic core of (−)-FR901483

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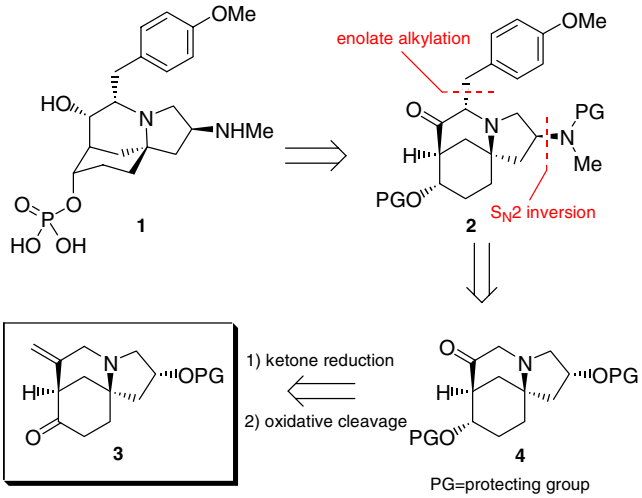
Abstract—An enantioselective synthesis of the tricyclic core structure of the immunosuppressant natural product (−)-FR901483 has been achieved. A palladium-catalysed ($Pd_2(dba)_3$, Xantphos, KOPh) intramolecular enolate alkenylation reaction was used as the key ring forming step for the construction of the bicyclo-[3,3,1]-azanonane ring system. An alkylidene carbene 1,5-CH insertion reaction was used to construct the nitrogen-bearing stereocentre in the vinyl bromide cyclisation precursor.

1. Introduction

(−)-FR901483 **1** was isolated from the fermentation broth of *Cladobotrym* sp. No. 11231 by researchers at the Fujisawa Pharmaceutical Company.[1] Its unusual chemical structure and novel immunosuppressant biological activity have combined to make **1** an appealing target for total synthesis.

A number of elegant total syntheses[2] and associated model studies[3] have been reported for **1**, and with the aid of these studies we disconnected **1** to reveal ketone **4** as an advanced synthetic precursor. As an alternative to aldol-based strategies, we decided to access **4** from alkene **3** in a similar manner to that reported by Wardrop in his excellent synthesis of racemic desmethylamino-FR901483.[2h] As all the steps required to convert **4** into the desired target have precedent in previous syntheses of **1**, we saw the asymmetric construction of the tricyclic alkaloid core **3** as the main challenge presented by **1** (Scheme 1). We now report our successful asymmetric synthesis of **3** and also describe some additional studies that have produced related tricyclic structures.

After considering several possible routes to **3**, we were particularly attracted to the use of a palladium(0)-mediated ketone α-alkenylation reaction to close the final bridged heterocyclic ring (viz **5**→**3**, Scheme 2)[4] in an analogous fashion to that recently reported in the racemic series by Bonjoch.[3e] We reasoned that cyclohexenone **5** could only form one cross-conjugated enolate,



Scheme 1.

and this design feature should eliminate the problems associated with the formation of regioisomeric tricycles encountered in Bonjoch's work.[3e] An alternative route to **3** that we wished to examine was based upon a possible 6-*endo*-trig radical cyclisation[5] of vinyl bromide **6** (Scheme 2).

In order to examine these two cyclisation strategies, we first needed to access the requisite vinyl bromide precursors **5** and **6**. During our total synthesis of the biosynthetically related natural product TAN1251A,[6] we demonstrated that the quaternary stereocentre present in the [6,5]-spirocyclic substructure (i.e., **7**, Scheme 2)

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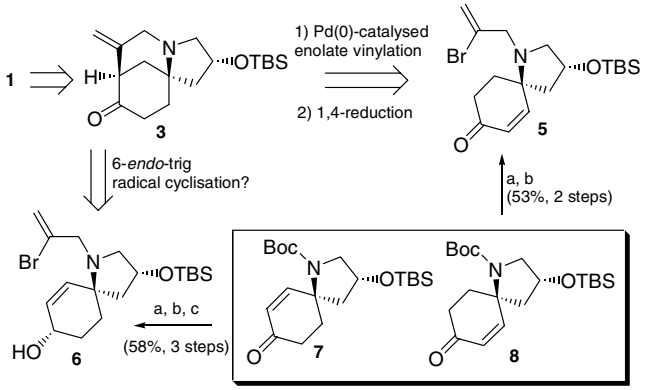
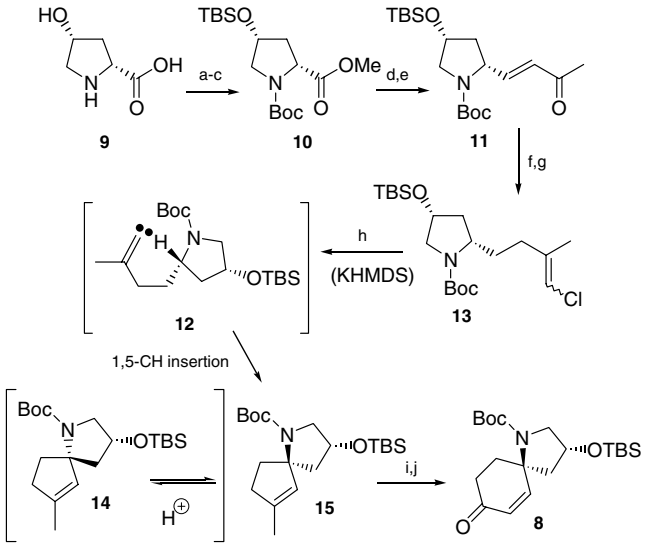


Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2; (b) 2,3-dibromopropene, K_2CO_3, LiI, MeCN; (c) $NaBH_4$, $CeCl_3$, MeOH.

could be accessed using an alkylidene carbene CH-insertion reaction and we saw the obvious potential to access the desired radical cyclisation precursor **6** from this material via simple N-alkylation and carbonyl reduction. Thus, deprotection of **7** (TFA, CH_2Cl_2) afforded an unstable amine–TFA salt, which was then immediately alkylated with 2,3-dibromopropene in the presence of K_2CO_3. Reduction of the resulting ketone then afforded the desired vinyl halide **6** in acceptable overall yield as a single diastereoisomer (Scheme 2).

The synthesis of the Pd(0)-enolate vinylation precursor **5** required access to the diastereoisomeric [6,5]-spirocycle **8**,[7] and this was readily accomplished via an analogous synthetic route to that previously used for the production of **7**.[6] Our first task was to prepare cyclopentene **15** from *cis*-hydroxyproline **9**. We were very pleased to find that the synthetic route previously optimised during the synthesis of **7**, worked very well in the revised diasteromeric series, and provided key cyclopentene **15** in good overall yield (Scheme 3).

As observed previously, the key alkylidene carbene 1,5-CH insertion reaction (**13**→**15**, Scheme 3) proceeded very cleanly (88%)[8] and gave a single diastereoisomer of cyclopentene product **15**. However, during the course of this work we found that trace amounts of HCl/DCl present in the $CDCl_3$ spectroscopic solvent were enough to induce epimerisation of **15** at the quaternary centre. The chemical shift of the olefinic proton in the ^1H NMR spectra of **15** and epimer **14** can be used to distinguish the two isomers (**15** shows a resonance at 5.10 ppm, whilst isomer **14** shows a resonance at 5.29 ppm in DMSO-d_6 at 80 °C). Fortunately this unwanted epimerisation could easily be avoided if either benzene or DMSO were used as the solvent during characterisation. Having secured a stereocontrolled route to cyclopentene **15** we were then able to effect an efficient ring expansion via an oxidative cleavage (OsO_4, $NaIO_4$)/aldol condensation (KOH/EtOH, then MsCl Et_3N) process to produce cyclohexenone **8** (Scheme 3). Finally, deprotection of **8** (TFA, CH_2Cl_2) and alkylation with 2,3-dibromopropene, in the presence of K_2CO_3, afforded the desired vinyl halide **5** in good yield (Scheme 2).

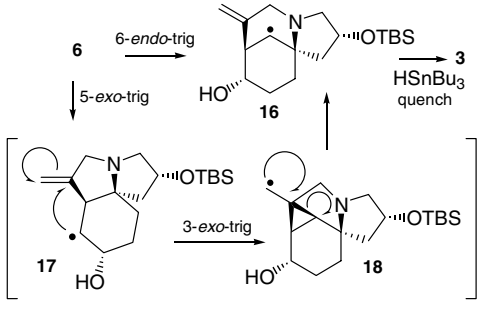


Scheme 3. Reagents and conditions: (a) AcCl, MeOH, 24 h; (b) Boc_2O, DCM, Et_3N, 0 °C, 27 h, 86%; (c) TBSCl, imidazole, DMF, 0 °C to rt, 27 h, 91%; (d) DIBALH, DCM, −78 °C, 3.5 h then MeOH, 1 h; (e) $Ph_3PCHCOCH_3$, DCM, 7 d, 82%; (f) H_2, Pd/C, EtOAc, 2 d, 98%; (g) KHMDS (0.5 M in toluene), $Ph_3PCH_2Cl_2$, THF, rt, 1 d, 89%; (h) KHMDS (0.5 M in toluene), Et_2O, 2 h, 88%; (i) NMMO, $K_2OsO_4{\cdot}2H_2O$ (3 mol %), acetone:H_2O (10:1), 6 d, 88%, then $NaIO_4$, THF:H_2O (2:1), rt, 2 h, 97%; (j) KOH, EtOH, 0 °C, 2 h, 96% then MsCl, Et_3N, DCM, rt, 24 h, 82%.

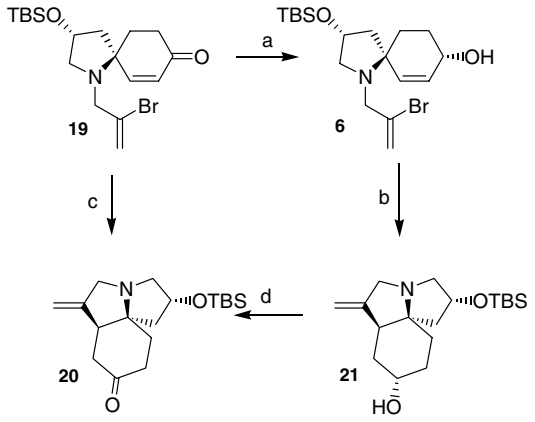
2. Radical cyclisation studies

Having successfully prepared both cyclisation precursors **5** and **6** we first chose to examine the radical cyclisation approach to **3**. Although 5-*exo*-trig cyclisations are usually favoured in competitive radical cyclisations, we hoped that a 6-*endo*-trig closure could be effected in this case due to the steric hindrance provided by the quaternary centre.[5] Even if the 5-*exo* cyclisation was kinetically favoured, we may be able to encourage a neophyl rearrangement (**17**→**18**→**16**, Scheme 4) to afford isomeric radical **16**, thus providing the desired six-membered heterocyclic product indirectly (Scheme 4).

In order to encourage the neophyl rearrangement to occur, the Bu_3SnH concentration must be kept sufficiently low so that radical **17** resulting from 5-*exo*-trig attack has enough time to rearrange to **16**, via **18**, before being quenched by Bu_3SnH.[9] With this in mind, a number of experiments were carried out, varying both the



Scheme 4. Mechanism of the proposed neophyl rearrangement.



Scheme 5. Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 90%; (b) and (c) Bu_3SnH, AIBN, benzene, 85% and 75%, respectively; (d) DMP, DCM, 0 °C to rt, 83%.

reaction concentration and rate of addition of Bu_3SnH. Unfortunately, however, even under very slow addition conditions (12 h) and low concentration of substrate **6** (e.g., 0.002 M), only the 5-*exo*-trig cyclisation product **21** (Scheme 5) was formed. Incomplete consumption of starting material **6** was observed in all reactions when the concentration of **6** was lower than 0.01 M, indicating premature termination of the radical chain reaction.

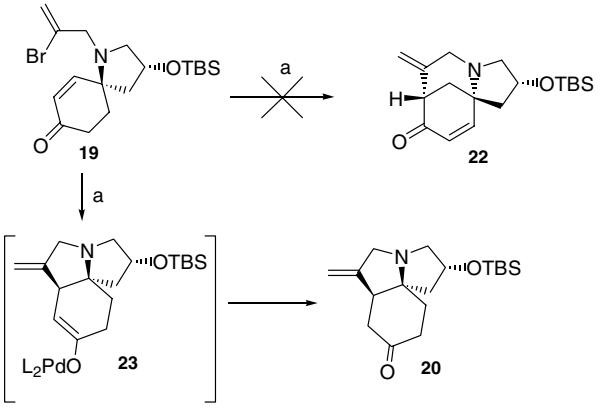
For completeness, radical cyclisation of **19**[10] was also attempted, but unsuprisingly only 5-*exo*-trig product **20** was obtained. Cyclohexanone **20** was also obtained from **21** by oxidation with the Dess–Martin periodinane (Scheme 5) thus confirming the structure of **21** formed during the earlier radical cyclisations (Scheme 5).

3. Pd-catalysed intramolecular alkenylation

Although we were not able to access the desired tricycle **3** via radical cyclisation, we were confident that intramolecular Pd(0)-catalysed enolate alkenylation[4] would be successful. As we had access to significant quantities of **19** remaining from the radical cyclisation attempts, we chose to use this as a model substrate with which to develop the enolate alkenylation conditions.

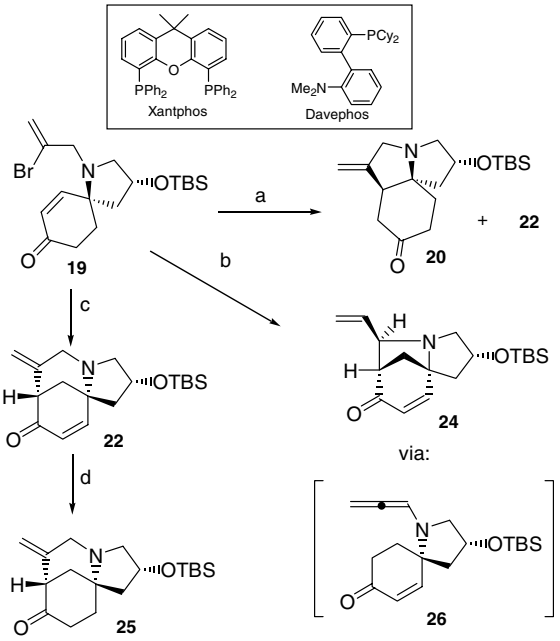
Initially we examined the $Pd(PPh_3)_4/KO^tBu$ catalyst system originally described by Bonjoch,[3e] but unfortunately these conditions failed to give the desired product **22**. Instead, tricycle **20** was formed in 23% yield, which is obviously the result of a Heck type reaction of the vinyl bromide with the enone. The saturated cyclohexanone is presumably formed via protonation of an intermediate palladium enolate species **23**. There is very little doubt about the structure of **20**, as its physical data were identical to those of the product already observed in the radical cyclisation studies (Scheme 6).

As $Pd(PPh_3)_4/KO^tBu$ failed to provide the desired tricycle **22**, we next examined the use of alternative catalysts derived from $Pd_2(dba)_3$ and a variety of alternative ligands (e.g., BINAP, Xantphos, DPPF, Davephos) and bases (e.g., NaO^tBu, NaOH, KOPh[4]).

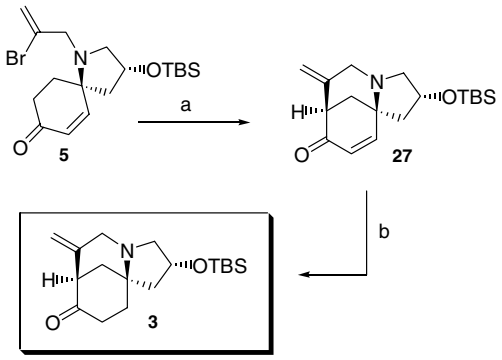


Scheme 6. Reagents and conditions: (a) $Pd(PPh_3)_4$, KO^tBu, THF (23%).

After extensive screening, we found that $Pd_2(dba)_3$/*rac*-BINAP[11]/NaO^tBu in THF (reflux) provided our first sample of the desired tricycle **22** in 25% yield, but it was also accompanied by the formation of the previously observed Heck-type product **20** (15%). In an attempt to optimise this reaction we examined the use of KOPh as base, whilst keeping all of the other conditions constant. To our surprise we found that the unusual tricycle **24** was produced as the only cyclised product,[12] and this presumably results from a palladium-catalysed cyclisation of an allene such as **26**. Fortunately, and after much further effort, we were able to obtain the desired tricyclic product **22** as the major new product (51%) with only trace amounts of **24**, by employing $Pd_2(dba)_3$/Xantphos/KOPh (prepared in situ from KO^t-Bu and PhOH) in THF (reflux) as the catalytic system.



Scheme 7. Reagents and conditions: (a) 10 mol % $Pd_2(dba)_3$, 30 mol % *rac*-BINAP, NaO^tBu, THF, reflux (**22**, 25% and **20**, 15%); (b) 10 mol % $Pd_2(dba)_3$, 30 mol % *rac*-BINAP, KOPh (57%); (c) 10 mol % $Pd_2(dba)_3$, 30 mol % Xantphos, KO^tBu/PhOH, THF, reflux, 4 h (51%); (d) Li, NH_3, then **22** added in THF, −78 to −33 °C, 3.5 h (75%).



Scheme 8. Reagents and conditions: (a) 10 mol % $Pd_2(dba)_3$, 30 mol % Xantphos, KO^{t}Bu/PhOH, THF, reflux, 7 h (43%); (b) Li, NH_3, then **27** added in THF, −78 °C, 4 h (67%).

Dissolving metal reduction (Li, NH_3/THF) of **22** then provided the desired bridged cyclohexanone **25** in good yield (75%), thus completing our model study (Scheme 7).

Having successfully developed a synthesis of **25**, we were keen to examine the synthesis of **3**, which is the stereoisomer required for our planned synthesis of (−)-FR901483. Thus, diastereoisomeric vinyl bromide **5** was subjected to the previously optimised Pd-catalysed intramolecular enolate alkenylation conditions, and we were pleased to observe that the required tricycle **27** was produced in 43% yield. Dissolving metal reduction of this tricyclic enone finally afforded the desired target **3** as a single stereo- and regioisomer (Scheme 8).

Work in our laboratory is now focussed upon further optimisation of the synthesis of **3**, and on the utilisation of this key intermediate for a total synthesis of (−)-FR901483. These studies will be reported in due course.

Acknowledgements

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References and notes

1. Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.
2. FR901483: (a) Brummond, K. M.; Hong, S. P. *J. Org. Chem.* **2005**, *70*, 907–916; (b) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729–2731; (c) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534–7538; (d) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125–1128; (e) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765–767; (f) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593–4596; (g) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778–7786, Desmethylamino-FR901483:; (h) Wardrop, D. J.; Zhang, W. M. *Org. Lett.* **2001**, *3*, 2353–2356; (i) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442–6443.
3. (a) Gotchev, D. B.; Comins, D. L. *J. Org. Chem.* **2006**, *71*, 9393–9402; (b) Kaden, S.; Reissig, H. U. *Org. Lett.* **2006**, *8*, 4763–4766; (c) Simila, S. T. M.; Reichelt, A.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 2933–2936; (d) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046–2055; (e) Bonjoch, J.; Diaba, F.; Puigbo, G.; Peidro, E.; Sole, D. *Tetrahedron Lett.* **2003**, *44*, 8387–8390; (f) Brummond, K. M.; Lu, J. L. *Org. Lett.* **2001**, *3*, 1347–1349; (g) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013–3015.
4. (a) Sole, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646–1650; (b) Sole, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749; For early examples of enantioselective intermolecular enolate alkenylations see: (c) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897–1900.
5. For a general discussion of 6-*endo*-trig radical cyclisations see: Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286, and references cited therein.
6. Auty, J. M. A.; Churcher, I.; Hayes, C. J. *Synlett* **2004**, 1443–1445.
7. An independent synthesis of a TBDPS-protected version of **8** via an enolate alkylation route has also been reported: Nagumo, S.; Matoba, A.; Ishii, Y.; Yamaguchi, S.; Akutsu, N.; Nishijima, H.; Nishida, A.; Kawahara, N. *Tetrahedron* **2002**, *58*, 9871–9877.
8. (a) Hayes, C. J.; Bradley, D. M.; Thomson, N. M. *J. Org. Chem.* **2006**, *71*, 2661–2665; (b) Hayes, C. J.; Sherlock, A. E.; Selby, M. D. *Org. Biomol. Chem.* **2006**, *4*, 193–195; (c) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613–7617; (d) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609–6611; (e) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011–6014; (f) Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 3541–3542; (g) Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377–3379; (h) Gabaitsekgosi, R.; Hayes, C. J. *Tetrahedron Lett.* **1999**, *40*, 7713–7716.
9. Neophyl rearrangements of this type are fast ($k \approx 10^7\ s^{-1}$) in comparison to hydrogen atom abstraction from ^{n}Bu$_3$SnH ($k \approx 10^6\ M^{-1}\ s^{-1}$) see: (a) Ingold, K. U. *Pure Appl. Chem.* **1984**, *56*, 1767–1779; (b) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.
10. Cyclohexenone **19** is the direct precursor to cyclohexenol **6**, whose preparation is shown in Scheme 2.
11. The use of enantiomerically pure (+)- and (−)-BINAP was also examined for this alkenylation reaction, but no improvement in yield or product distribution was observed over *rac*-BINAP.
12. The relative stereochemistry of **24** was unambiguously determined using ^{1}H NMR NOE experiments.