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Macrocyclic Ring Closures Employing The Intramolecular Heck Reaction.

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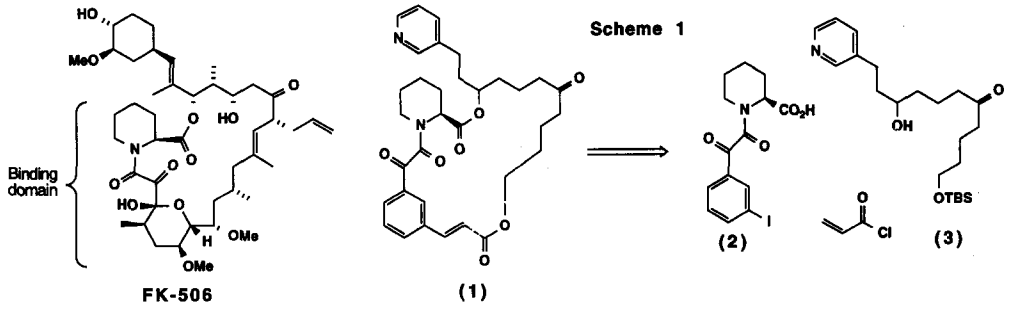
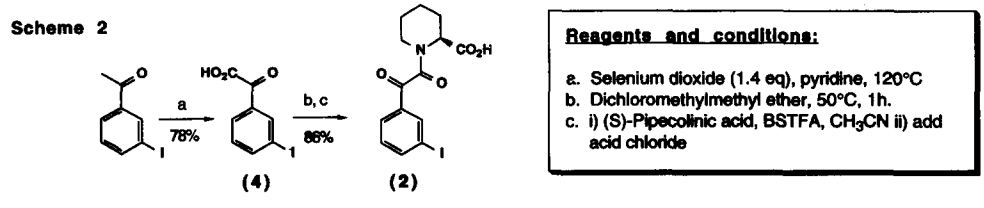
Abstract: Intramolecular Heck reactions have been employed for the final ring closure step in the construction of a series of macrocyclic compounds.

In our ongoing investigations into novel synthetic immunomodulators based upon FK-506[1] we wished to prepare macrocyclic compounds such as **1**, that contained a binding region as well as an effector region (the so called "dual-domain" compounds)[2]. It has been shown by ourselves[3] and other groups[4] that replacement of the complex pyranoside group in FK-506 for an aromatic ring affords compounds that have a reasonably good affinity for FKBP12[5]. For our initial target we chose compound **1** which possesses a cinnamate functionality linked *via* a functionalised spacer group to a pipecolinate unit. Furthermore, we envisaged that compounds of this type could be constructed by employing an intramolecular Heck reaction[6] for the formation of the macrocyclic ring. The key to the synthesis of **1** lay in the preparation of acid **2** and the secondary alcohol **3**[7] (Scheme 1).

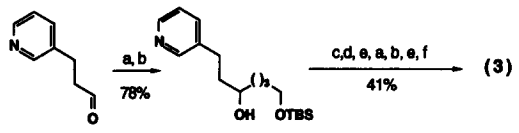


m-Iodoacetophenone was oxidised to the ketoacid **4** *via* oxidation with selenium dioxide in pyridine[8]. On a multigram scale, 10% of the decarbonylated adduct was observed, however, this was easily removed by recrystallization to afford pure **4**. The keto-acid **4** was coupled *via* it's acid chloride[9] to (S)-pipecolinic acid under standard conditions to afford acid **2** in high overall yield (Scheme 2).



The acid's coupling partner, alcohol **3**, was prepared by addition of the Grignard reagent derived from 4-chlorobutanol[10] to pyridine-3-propanal[11] with subsequent functional group manipulation (Scheme 3).

Scheme 3

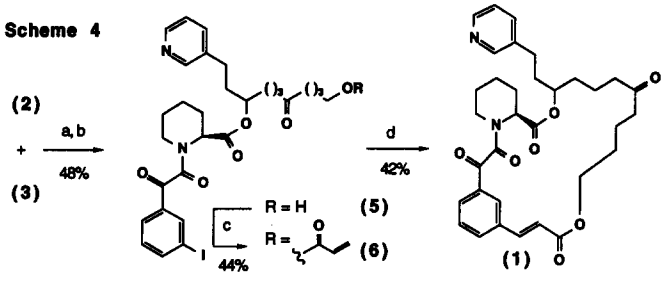


Reagents and conditions:

a. $ClMgCH_2CH_2CH_2CH_2OMgCl$, THF, -10°C
b. TBSCl, DMAP, NEt_3, CH_2Cl_2
c. Benzoic acid, DCC, DMAP, CH_2Cl_2
d. HF, CH_3CN
e. DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -65°C
f. NaOH, H_2O, MeOH

Standard DCC esterification[12] of alcohol **3** with acid **2** followed by deprotection with HF in acetonitrile afforded alcohol **5** that was esterified under standard conditions to afford acrylate **6** as a 1:1 mixture of 2 diastereomers. Exposure of the acrylate to the Heck conditions as outlined by Gaudin[13] [palladium (II) acetate, tri-*o*-tolylphosphine and triethylamine in acetonitrile at 85°C][14] afforded the product **1** in 42% yield (Scheme 4).

Scheme 4

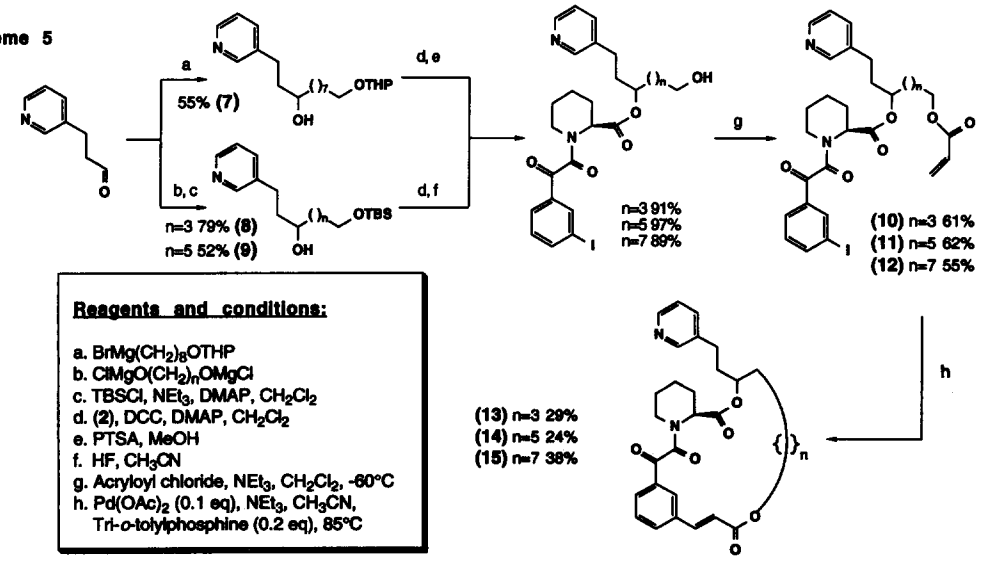


Reagents and conditions:

a. DCC, DMAP, CH_2Cl_2
b. HF, CH_3CN
c. Acryloyl chloride, NEt_3, CH_2Cl_2, -60°C
d. $Pd(OAc)_2$ (0.1 eq), NEt_3, CH_3CN, Tri-*o*-tolylphosphine (0.2 eq), 85°C

We decided to investigate the reaction further and prepared a series of alcohols (**7**, **8**, **9**) with variation in the length of the side chain. After esterification with acid **2**, subsequent functional group manipulation afforded the series of macrolide precursors (**10**, **11**, **12**). Employing the same conditions as before, the cyclisations occurred in reasonable yields (Scheme 5).

Scheme 5

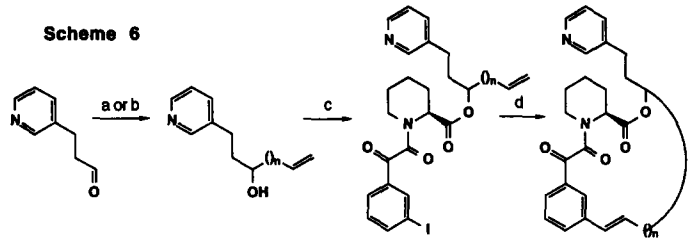


Reagents and conditions:

a. $BrMg(CH_2)_8OTHP$
b. $ClMgO(CH_2)_nOMgCl$
c. TBSCl, NEt_3, DMAP, CH_2Cl_2
d. (2), DCC, DMAP, CH_2Cl_2
e. PTSA, MeOH
f. HF, CH_3CN
g. Acryloyl chloride, NEt_3, CH_2Cl_2, -60°C
h. $Pd(OAc)_2$ (0.1 eq), NEt_3, CH_3CN, Tri-*o*-tolylphosphine (0.2 eq), 85°C

We decided to briefly examine the role of the olefin in the cyclisation and prepared the unactivated terminal olefins (**18** and **19**). Compounds **16** and **17** were prepared by treating 3-pyridine propanal with the Grignard reagents derived from 8-bromo-1-octene and 10-bromo-1-decene. Esterification of the resulting alcohols **16** and **17** with acid **2** afforded the cyclisation precursors **18** and **19**. Cyclisation of these compounds under the same Heck conditions once more afforded macrocyclic compounds in reasonable yields (Scheme 6).

Scheme 6



(16) n=6 49%
(17) n=8 53%

(18) n=6 72%
(19) n=8 77%

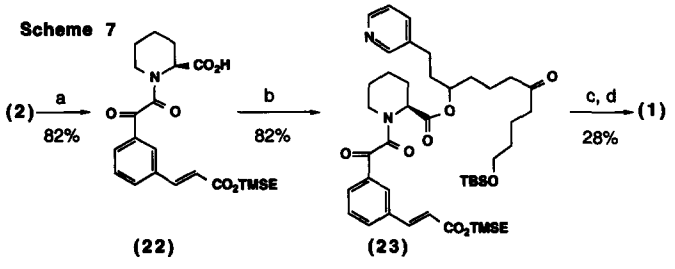
(20) n=6 24%
(21) n=8 16%

Reagents and conditions:

a. $BrMg(CH_2)_6CHCH_2$, THF, 0°C
b. $BrMg(CH_2)_6CHCH_2$, THF, 0°C
c. (2), DCC, DMAP, CH_2Cl_2
d. $Pd(OAc)_2$ (0.1 eq), NEt_3, CH_3CN, Tri-*o*-tolylphosphine (0.2 eq), 85°C

It was decided to compare this cyclisation strategy with a ring closure procedure employing a macrolactonisation. Thus acid **2** was converted to the trimethylsilylethyl acrylate[15] **22** by an application of the mild solid-liquid phase transfer conditions outlined by Jeffery[16]. Esterification of the resulting acid **22** with alcohol **3** afforded diester **23**. Concomittant deprotection of the acid and alcohol groups followed by macrocyclisation afforded the adduct **1** in 28% yield (Scheme 7).

Scheme 7



(22) **(23)**

Reagents and conditions:

a. Acrylate (5eq), $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, rt, 20h.
b. Alcohol (3), DCC, DMAP, CH_2Cl_2
c. TBAF, THF
d. EDCI.HCl, DMAP.HCl, DMAP, $CHCl_3$, high dilution syringe pump addition, 70°C

To the author's knowledge this is the first reported case of an intramolecular Heck reaction to be applied in the formation of a macrocyclic ring. We have demonstrated that the reaction is applicable to variation in macrocycle size (rings of 16 to 22 atoms have been formed) and variation in the nature of olefin has been demonstrated. It is interesting to note that in the case of the styrene adducts (**20** and **21**), only the (E) olefin isomer was observed[17]. We believe that this reaction is applicable to a wide range of substrates and that the mild reaction conditions (no epimerisation of amino acids observed) offers scope for this reaction to be applied towards natural product syntheses. Thus, although the reaction is at present unoptimised, it offers considerable scope for further synthetic strategies.

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14. **Typical experimental conditions**: To a solution of the acrylate **6** (136 mg, 0.194 mmol) in acetonitrile (5 ml) and triethylamine (1 ml) was added palladium(II)acetate (4.6 mg, 0.0194 mmol) and tri-*o*-tolylphosphine (11.8 mg, 0.0387 mmol). The reagents were sealed in a reaction vial and heated to 85℃ for 2h. During this time a palladium mirror was deposited on the glass and this signified the end of the reaction. The mixture was cooled, concentrated and the residues purified by chromatography on silica gel eluting with ethyl acetate to afford the product **1** (46 mg, 42%) as an oil: m/z (FAB) 575 (M+H), 307, 262, 186, 154.
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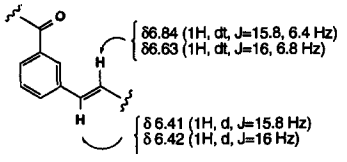
For example, in **20** (mix. of 2 diastereomers), the 500 MHz ^{1}H nmr spectrum shows solely the (E) geometry of the styrene.



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