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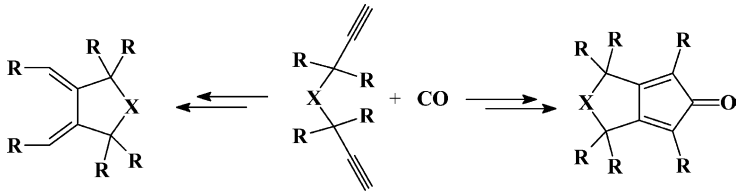
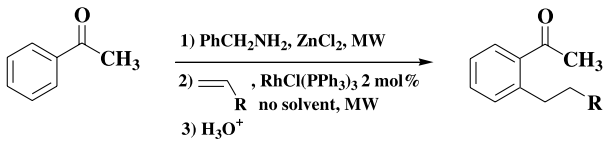
Contents

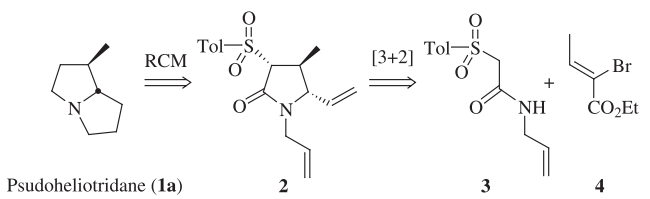
REPORT

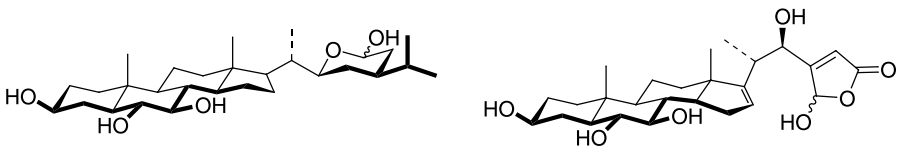


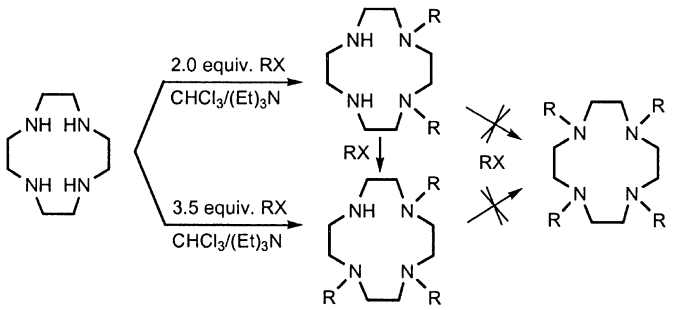
Recent progress in the preparation of heterocycles by carbonylation of acetylenic hydrocarbons, alcohols, organic halides and other substrates catalysed by transition metals, salts of transition metals and organometallic complexes are reviewed. The synthesis of new carbonyl-, carboxyl- and alkoxycarbonyl- containing compounds including the creation or modification of heterocycles are discussed.

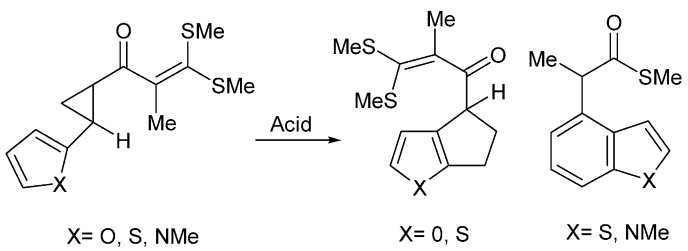
ARTICLES

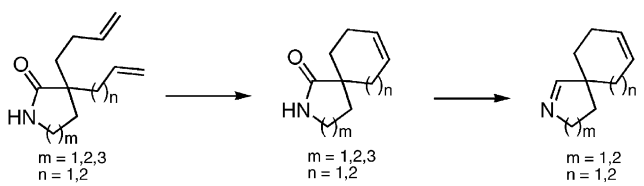


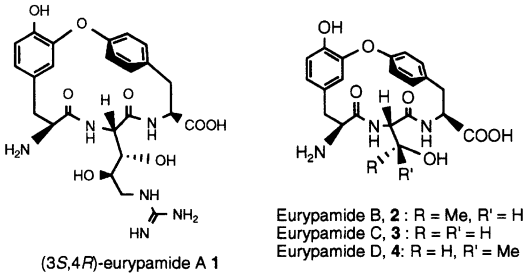


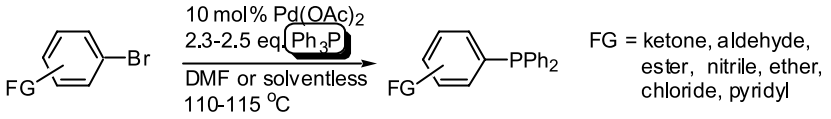












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Synthesis of heterocycles by carbonylation of acetylenic compounds

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1. Introduction

The carbonylation of unsaturated hydrocarbons, alcohols, organic halides and other substrates catalysed by transition metals, salts of transition metals and organometallic complexes is a widely used method for the synthesis of new carbonyl-, carboxyl- and alkoxycarbonyl- containing compounds including the creation or modification of heterocycles.[1–9] The information on the synthesis of heterocycles by carbonylation of acetylenic compounds in previous references is, however, practically absent and many of these have appeared more than 25 years ago. In the present review, we present the latest data on the preparation of various heterocyclic compounds.

2. Synthesis of alkoxycarbonyl derivatives of dimethylenepyrrolidines

It was found by Chiusoli et al.[10,11] that α,α-tetraalkyl-substituted dipropargylamines react with carbon monoxide and alcohols or water in the presence of a $PdCl_2$-thiourea complex, forming the alkoxycarbonyl derivatives of dimethylenepyrrolidines (**1**,**2**) (Scheme 1).

When $PdCl_2$ was used as a catalyst in the presence of carbon monoxide (CO/O_2=90:10) in methanol, dimethoxycarbonyl dimethylenepyrrolidines (**3** and **4**) were mainly formed. The monomethoxycarbonyl derivatives **1** and **2** were produced as byproducts. A similar pattern occurred if the reaction was catalysed by Pd^0/C in the presence of KI and oxygen (CO/O_2=94:6). On the other hand, the stereoisomeric, dimethoxycarbonyl dimethylene-pyrrolidine (**5**), was also obtained in low yield[12] (Scheme 2).

Upon oxidative alkoxycarbonylation of dipropargylamines and amides using a mixture of CO/air at **4** bar pressure in an alcohol in the presence of a Pd^0/C catalyst and KI, the 3,4-bis(alkoxycarbonylmethylene)pyrrolidines **6** were obtained. The isomerisation of **6** under various conditions leads to the formation of pyrroles **7** and free pyrrole-3,4-diacetic acid **8**[13] (Scheme 3).

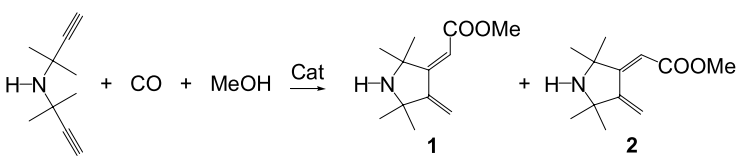
3. Synthesis of alkoxycarbonyl derivatives of tetrahydropyridine

In addition to the $PdCl_2$-catalysed oxidative methoxycarbonylation reactions of *N*,*N*-dipropargyl-arylamines by carbon monoxide in methanol, $PdCl_2$ in the presence of $CuCl_2$ and NaOAc as co-catalysts can be used to produce the cyclic compounds, the dimethyl-1-aryl-5-methoxycarbonylmethylene-1,2,5,6-tetrahydro-pyridine-3,4-dicarboxylates **10**. In some cases, **10** were produced together with the byproducts, the alicyclic diesters of aminodicarboxylic acids **9** (Scheme 4).[14,15]

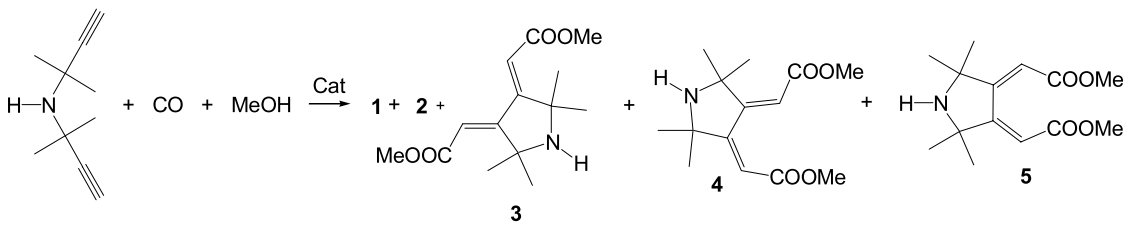
The formation of the cyclic aminotriesters **10** takes place by additive methoxycarbonylation of one of the triple bonds of the arylaminodiesters **9**, followed by cyclisation. The formation of the cyclic compounds **10** and the arylaminodiesters **9** is dependent on the nature and position of the substituent X in the aryl ring (when X=*p*-Me, *p*-OMe and *p*-Br no traces of the cyclic compound **10** were observed) and, apparently, the stability of the intermediate complexes of the arylaminodiesters **9** with the catalyst $PdCl_2$ determines the reaction course.[15]

4. Synthesis of tetrahydrofuran and pyrrolidine derivatives

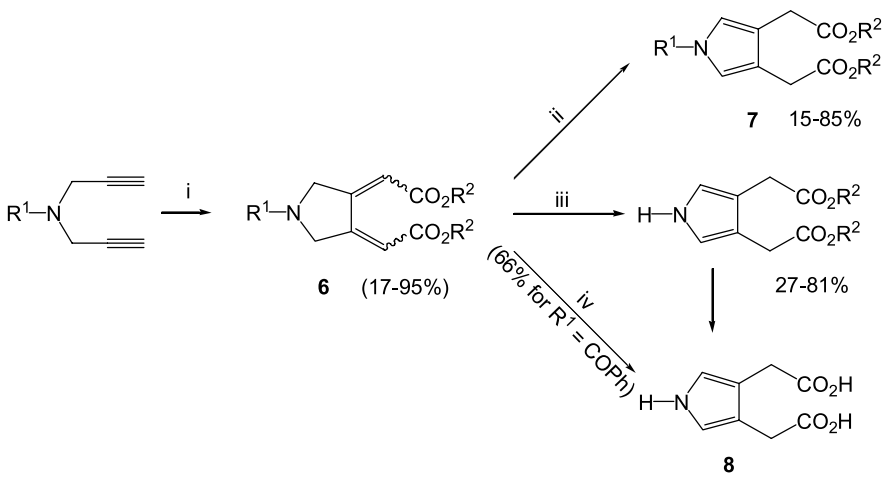
The intramolecular silylcarbocyclisation (SiCaC) of 1,6-enynes **11** catalysed by Rh or Rh–CO complexes leads to the tetrahydrofuran and pyrrolidine derivatives **12** in high yields[16,17] (Scheme 5). Under a high pressure of CO



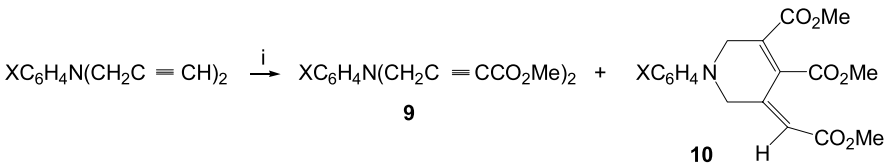
Scheme 1.



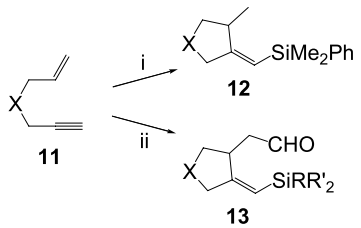
Scheme 2.



Scheme 3. R^1=alkyl, aryl, alkoxycarbonyl, tosyl; R^2=alkyl. (i) CO/air, R^2OH, Pd/C, KI; (ii) DMSO or MeCN/Et_3N, 25–70 °C, 3–70 h, (iii) R^2OH, Et_3N, 25–80 °C, 5–70 h; (iv) (1) $Ba(OH)_2/H_2O$, 100 °C, 15 h, (2) H_2SO_4/H_2O; (v) (1) NaOH/H_2O, 100 °C, 30–40 min, (2) H_2SO_4/H_2O, 0 °C.



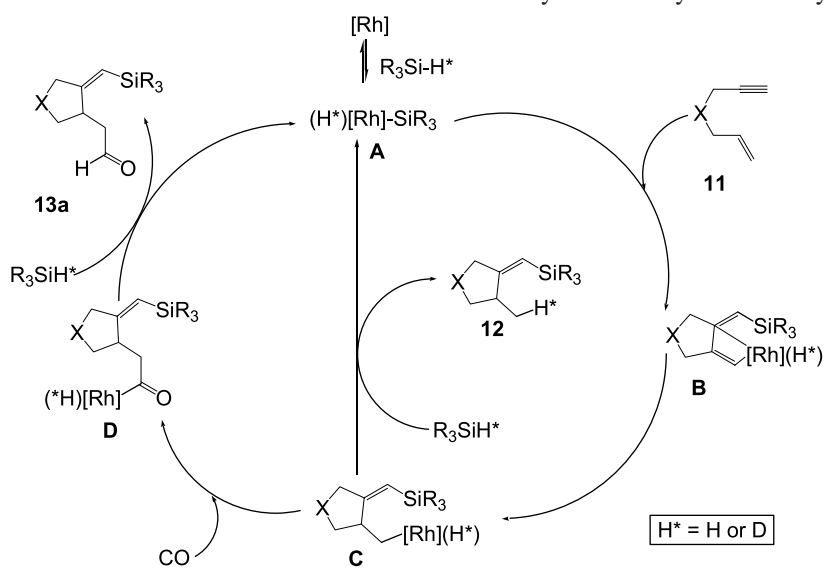
Scheme 4. (i) CO, MeOH, $PdCl_2$ (10 mol%), $CuCl_2$ (4 equiv.), NaOAc (1 equiv.). Compound **10**: X=H (11%), *p*-Cl (36%), *m*-Cl (40%), *m*-Br (47%), *o*-Cl (24%), *o*-Br (45%).



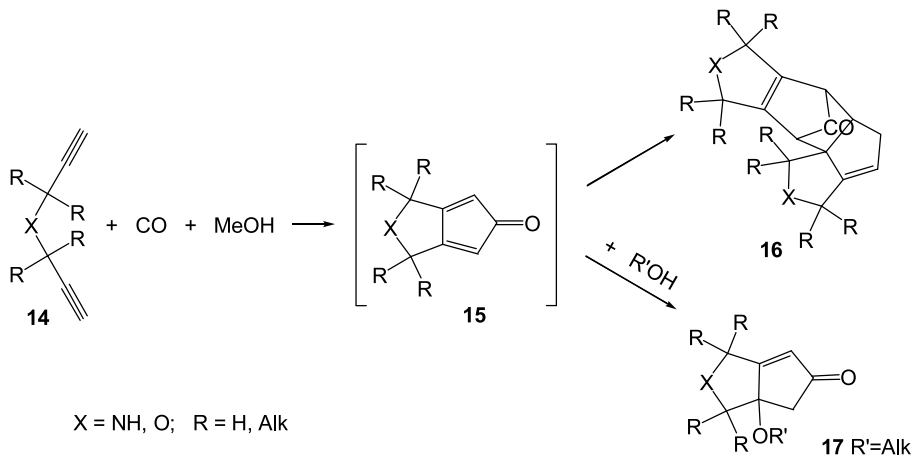
Scheme 5. (i) [Rh] cat. (0.5 mol%), $PhMe_2SiH$ (1–1.5 equiv.); CO (1 atm), toluene or hexane, 22 or 70 °C; (ii) [Rh] cat (0.5 mol%), $P(OEt)_3$ (10 mol%), RR′SiH (1–1.05 equiv.); CO (10–20 atm), toluene or dioxane, 65–105 °C. Compound **12**: cat.—$Rh(acac)(CO)_2$; X=O (82%); cat.—$Rh_4(CO)_{12}$, X=NCH_2CH=CH_2 (74%); X=NCHMePh (89%); X=NBr (83%); X=NTs (86%). Compound **13**: cat.—$Rh(acac)(CO)_2$; R=R′=Et, X=O (15–20%); cat.—$Rh_4(CO)_{12}$, R=Ph, R′=Me, X=NTs (86%); X=NMs (56%).

(10–20 atm), the SiCaC reaction of allylpropargyl ether or allylpropargylamines with Et_3SiH or Me_2PhSiH catalysed by $Rh(acac)(CO)_2$ or $Rh_4(CO)_{12}$ with the addition of 10 mol% $P(OEt)_3$ took place to give the corresponding exo-silylmethylene tetrahydrofuran and pyrrolidine derivatives **13** bearing a formylmethyl moiety at the C-2 position in high yields (Scheme 5).[16,17]

The most plausible mechanism for the silylcarbocyclisation of the enynes **11**, which can accommodate the formation of both SiCaC products **12** and CO–SiCaC products **13a**, is proposed in Scheme 6. The silylcarbocyclisation of enynes should begin with the formation of the active catalyst species, the silyl-[Rh] complex **A**, followed by insertion of the acetylene moiety of the enyne **11** to generate the



Scheme 6.



Scheme 7.

β-silylvinyl-[Rh] complex **B**. Coordination of the olefin moiety, followed by intramolecular carbometallation, leads to the formation of the *exo*-methylenecyclopentylmethyl-[Rh] complex **C**. In the absence of CO or at a very low concentration of CO, hydrosilane-promoted reductive elimination takes place, to give the SiCaC product **12** and regeneration of the silyl-[Rh] complex **A**. At higher CO concentrations, migratory insertion of CO into the alkyl-[Rh] bond of **C** occurs, leading to the formation of the acyl-[Rh] complex **D**. Subsequent hydrosilane-promoted reductive elimination affords the CO–SiCaC product **13a** and regenerates the active catalyst species **A**. A CO atmosphere is not essential for the SiCaC process. The use of a CO atmosphere however, appears to stabilise the active [Rh] catalyst species, especially when the Rh carbonyl clusters are used for a prolonged period of time.

5. Polycyclic heterocycle formation

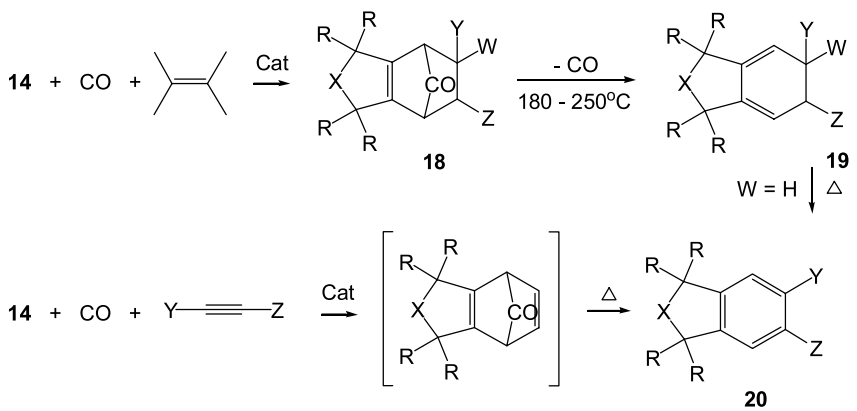
Chiusoli and co-workers have found, that the polycyclic products **16** were formed by carbonylation of the 1,6-diynes **14** in the presence of Pd^0 on charcoal[18] (Scheme 7).

The reaction proceeded at room temperature and at atmospheric pressure of carbon monoxide and the polycyclic compounds **16** were formed by dimerisation of the cyclopentadienone **15**. When the reaction is carried out in a base/alcohol medium (X=NH, NMe; R=alkyl), the cyclopentadienone **15** is attached by an alkoxyl group with the formation of the corresponding alkoxycyclopentenones **17**. Utilising various alkenes and alkynes as dienophiles allowed a further extension to the new types of heteropolycyclic compounds **18**-**20** (Scheme 8).[19]

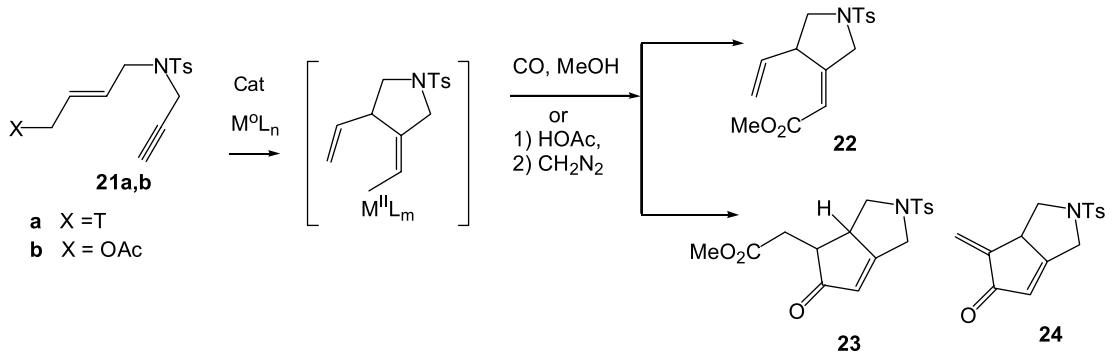
Palladium on charcoal (10%), and other Pd^0 complexes such as $Pd_2(dba)_3$ (dba=dibenzylideneacetone) or palladium salts and metallic Pd are used as catalysts. Heating the alkynes as dienophiles spontaneously furnished the aromatic products. The best yields were obtained for the polycyclic compounds **18** and **20** (up to 98%) using alkynes and alkenes with terminal double and triple bonds. In the absence of CO, under the same conditions, the reactions did not proceed, but using Ni and Co complexes as catalysts, the cycloaromatisation reaction of the dialkynes **14** proceeded smoothly.[20]

6. Highly stereoselective cyclisation/carbonylation of alkynylallylamines

Oppolzer et al. have shown that catalysts comprising nickel or palladium complexes promote a highly stereoselective cyclisation/carbonylation reaction of the propargylallylamines



Scheme 8. X=NH, NCO_2Me, NCOPh, O; Y=Ph, CO_2Me, H, CN, $CH=CH_2$; Z=H, Me, CO_2Me; W=H, Me, CO_2Me.

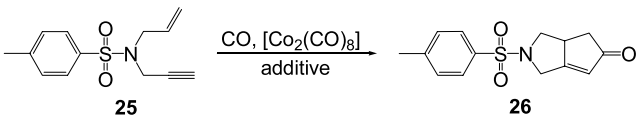


Scheme 9.

Table 1. Nickel(°)/and palladium(°) catalysed cyclisation/carbonylation of amines **21a**,**b**

N	21	Catalyst	Reaction conditions (time, h)	Products (yields, %)		
				22	23	24
1	**A**	$Ni(CO)_3PPh_3$	A (20)	69	—	—
2	**A**	$Ni(cod)_2$/dppb	A (12)	23	57	—
3	**B**	$Pd(dba)_2/PPh_3$	B (2)	13	50	16

A: 25 mol%Ni(0), THF/MeOH 4:1, CO (1 atm), rt. B: 10 mol% Pd(0), HOAc, CO (1 atm), 45 °C.

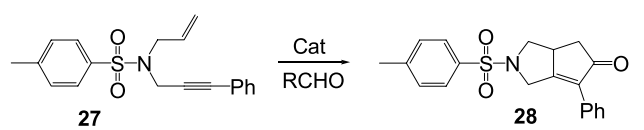


Scheme 10.

Using an intramolecular catalytic Pauson–Khand reaction (CPKR) of the propargylallylamide of *p*-toluenesulphonic acid **25** with octacarbonyldicobalt(°) catalyst the bicyclic derivative of pyrrolidine **26** has been prepared[23–27] (Scheme 10, and entries 1–3 in Table 2). 1,2-Dimethoxyethane (DME) was found to be the best promoter, giving the cycloaddition products in very good yields (Table 2, entry 3).[25] A catalytic conversion of the enyne **25** into **26** employing phosphites as coligands was reported by Jeong and coworkers (Table 2, entry 4).[26] Remarkably, under 1 atm of CO, the use of phosphites as coligands did not show any positive effect on the CPKR conversions. A disadvantage of this procedure is that it takes place only at apparent pressures of 3 atm. Kraft et al. used cyclohexylamine ($CyNH_2$) as an additive for the thermal CPKR (Table 2, entry 5). They developed a set of conditions that avoided the need for rigorous purification of the $[Co_2(CO)_8]$.[24] Hashimoto and coworkers have proved that the addition of phosphine sulphides to the CPKR improved the reaction

Table 2. Influence of different additives on the cobalt-catalysed Pauson–Khand reaction

Entry	$Co_2(CO)_8$ (mol%)	Additive (mol%)	T (°C)	p CO (atm)	Solvent	Reaction time (h)	Yield of **26** (%)	Ref.
1	7.5	None	60	1	DME	12	86	23
2	10	None	70	1	DME	10.5	63	24
3	3	DME (12)	120	7	Toluene	10	84	25
4	5	$P(Oph)_3$ (20)	120	3	DME	24	94	26
5	10	$CyNH_2$ (20)	70	1	DME	14	89	24
6	5	Bu_3PS (30)	70	1	Benzene	4	87	27



Scheme 11.

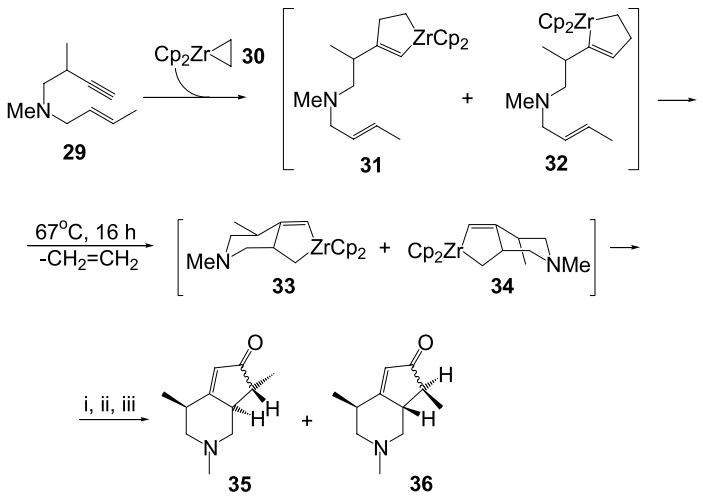
21a,**b**, which furnished the mono- **22** and bicyclic **23**,**24** derivatives of pyrrolidines (Scheme 9), depending on the catalyst used and the reaction conditions[21,22] (Table 1).

yield, and a faster conversion under 1 atm of CO was attained (Table 2, entry 6).[27]

More recently, two independent research groups have reported the use of aldehydes as a CO source for the Pauson–Khand reaction of the alkynylallylamide **27** to produce **28** (Scheme 11, and Table 3).[28,29] In a search for CO-transfer catalysts, Morimoto et al. tested different aromatic aldehydes with Rh, Ir and Ru species. They found that the most active system was a combination of the complex $[\{RhCl(cod)\}_2]$ (0.05 equiv.) with C_6F_5CHO

Table 3. CPKR using aldehydes as CO source

Entry	Catalyst (mol%)	Additive (mol%)	RCHO	Solvent, atmosphere	T, (°C)	Reaction time (h)	Yield of **28** [mol %]
1	$[Rh(cod)]_2$ (5)	dppp (11)	C_6F_5CHO (2 equiv.)	Xylene, N_2	130	4	95
2	$Rh(dppp)_2Cl$ (5)	—	cinnam-aldehyde (20 equiv.)	—, Ar	120	2	98



Scheme 12. (i) CO, −78 °C, 2 h; (ii) I_2 (2 equiv.), −78 °C to rt; (iii) MeOH/$NaHCO_3$ aq.

(2 equiv.), and several enynes could be cyclised under a nitrogen atmosphere (Table 3, entry 1).[28]

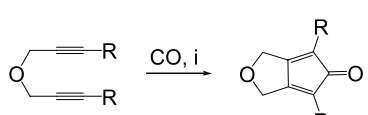
Shibata et. al. tested different aldehydes in a solvent-free system, employing the rhodium species $[Rh(dppp)_2Cl]$ (dppp=1,3-bis(diphenylphosphinyl)propane as a catalyst.[29] In this case, cinnamaldehyde was the most efficient aldehyde among those tested. The reactions were carried out employing 0.05 equiv. of the catalyst under 1 atm of argon (Table 3, entry 2).

Reaction of the enyne **29** catalysed by the in situ-generated zirconocene ethylene **30** at room temperature afforded the monocyclic products **31** and **32** (3:1). Heating at reflux in THF for 3 h gave complete conversion to the zirconabicycles **33** and **34**. Carbonylation (1 atm CO, rt 16 h) furnished an easily separable 4:1 mixture of (±)-tecomanine **35** and (±)-4-*epi*-tecomanine **36** in a non-satisfactory 21% overall yield based on **29** (Scheme 12). The yield was slightly increased to 31% by carrying out the carbonylation at −78 °C for 2 h and then working up with iodine (2 equiv.).[30]

7. Synthesis of bicyclic derivatives of tetrahydrofuran

The iridium complex-catalysed carbonylative alkyne–alkyne coupling provides bicyclopenta-dienones **37** in high isolated yields. Among the examined iridium complexes and phosphine ligands, IrCl(cod)(dppp) and $IrCl(CO)(PPh_3)_2$ (Vaska's complex) gave the best results (Scheme 13).[31,32]

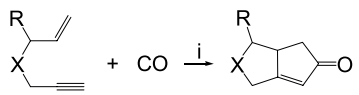
An intramolecular catalytic cycloaddition reaction of alkynylalkenylic ethers or amines and carbon monoxide



37 a R = $SiPh_3$ (78%)
b R = Ph (65%)

Scheme 13. (i) Ir complex (10 mol%), CO (1 atm), xylene, reflux.

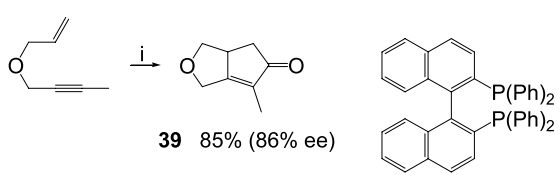
employing catalytic amount of $Co(acac)_2$ and $NaBH_4$ was developed for the synthesis of heterocyclic derivatives of cyclopentenone **38a-c**[33] (Scheme 14).



38a-c
a X = NTs; R = H (85%)
b X = O; R = $CH_2OTBDPS$ (82%)
c X = O; R = H (59%)

Scheme 14. (i) Co(acac) (0.05–0.1 mol), $NaBH_4$ (0.1–0.2 mol%), CO (30–40 atm), CH_2Cl_2, 100 °C, 48 h.

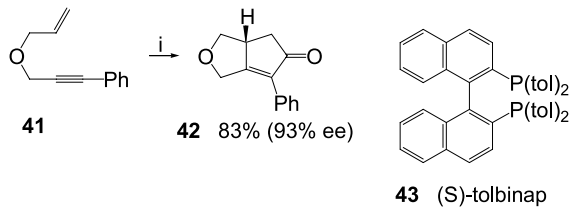
Jeong and co-workers recently reported an asymmetric rhodium-based catalytic system for the synthesis of bicyclic derivatives of tetrahydrofuran **39**.[34] The conditions were optimised with respect to the partial pressure of carbon monoxide, reaction temperature, and time. Good to very good *ee* values were found for a small range of intramolecular substrates when treated with $[RhCl(CO)_2]_2$ (0.03 equiv.), (*S*)-binap **40** (0.09 equiv.) and AgOTf (0.12 equiv.), as shown in Scheme 15.



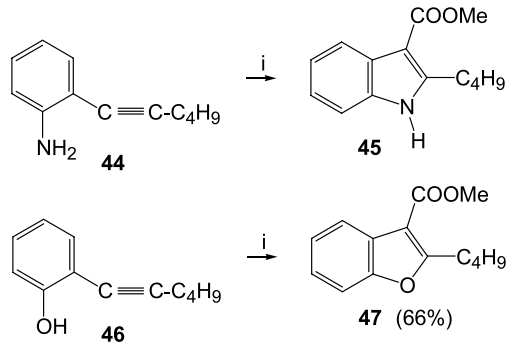
39 85% (86% ee)
40 (S)-binap

Scheme 15. (i) (*S*)-Binap **40** (0.09 equiv.), $[RhCl(CO)_2]$ (0.03 equiv.), AgOTf (0.12 equiv.), THF, 130 °C, 20 h, CO (2 atm).

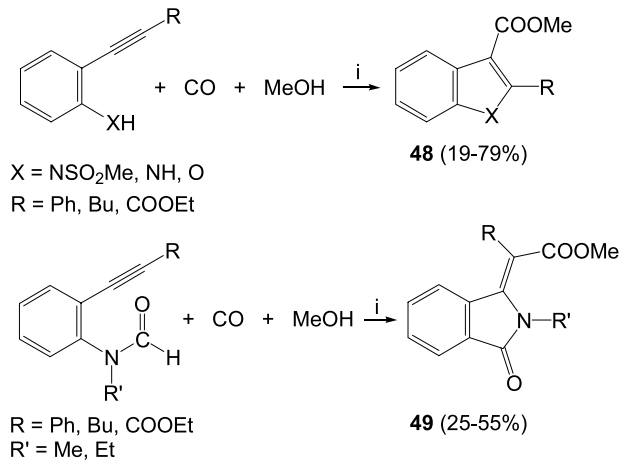
Shibata and Tagaki have studied the catalytic effect of $[Ir(cod)Cl]_2$ for the cyclisation of the allylalkynyl ether **41**.[35] They observed that the addition of phosphanes as coligands improved the yields of the reaction, and decided to use (*S*)-tolbinap **43** as an additive ligand. Excellent yields



Scheme 16. (i) (*S*)-Tolbinap **43** (0.2 equiv.), $[Ir(cod)Cl]_2$ (0.1 equiv.), toluene (0.12 equiv.), reflux, 18 h, CO (1 atm).



Scheme 17. (i) CO, MeOH, NaOH, $PdCl_2$, $CuCl_2$.



Scheme 18. (i) $PdCl_2$, $CuCl_2$, NaOAc (or K_2CO_3), 3 h, 20 °C.

and enantiomeric excesses of the bicyclic derivative of tetrahydrofuran **42** were obtained (Scheme 16).

8. Synthesis of indoles and benzofurans

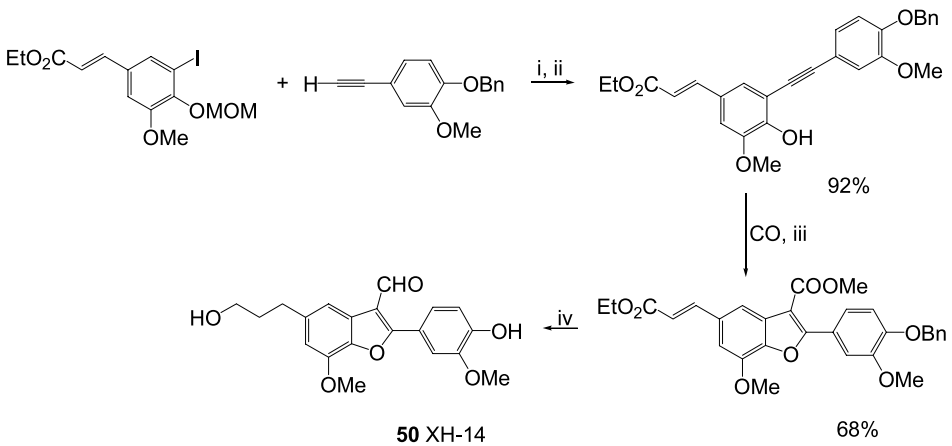
Palladium chloride-catalysed carbonylation of the *o*-hexynylaniline **44** and -phenol **46** produced the methyl 2-butylindole-3-carboxylate **45** and methyl 2-butylbenzofuran3-carboxylate **47**, respectively[36] (Scheme 17).

The reaction mechanism includes the formation of an intermediate bicyclic Pd complex, followed by carbonylating with CO into an acylpalladium complex. Treatment with methanol furnished the final product and a Pd^0 species. The catalyst regeneration as Pd^0 occurred by Pd^{2+} oxidation with participation of $CuCl_2$.[36]

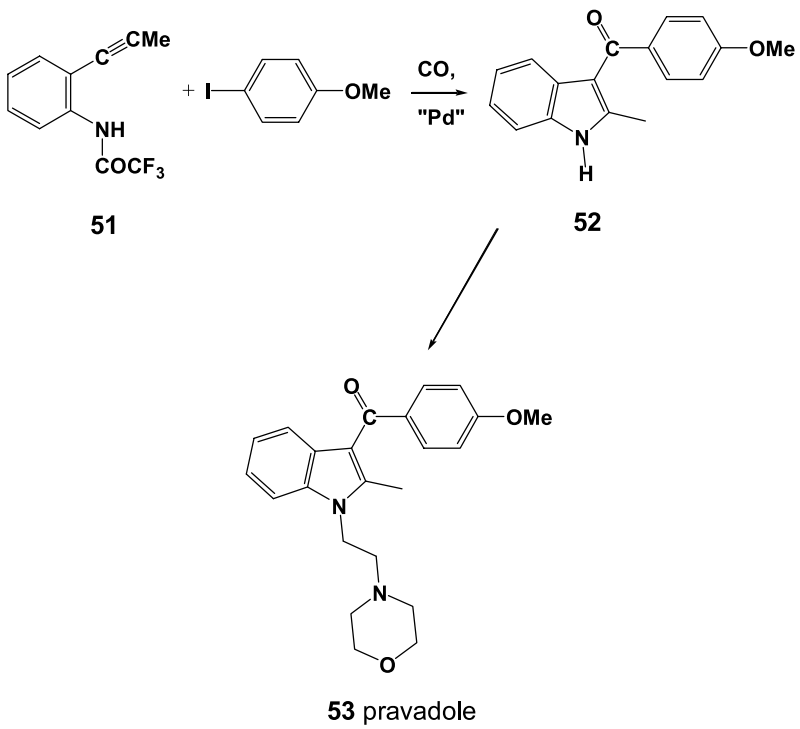
More recently, the reaction cycle has been extended, and a series of 2-substituted 3-methoxy-carbonylindoles and benzofurans **48** has been obtained. Only the lactams **49** have been formed from the 2-alkynylformanilides under these conditions[37] (Scheme 18).

A related synthetic strategy has been used to prepare the natural product XH-14 **50**, which possesses a benzo[*b*]furan skeleton. The synthesis involved the use of palladium-catalyzed cyclisation, with concomitant carbonylation via insertion of carbon monoxide, to introduce regioselectively a formyl group in the 3-position[38] (Scheme 19).

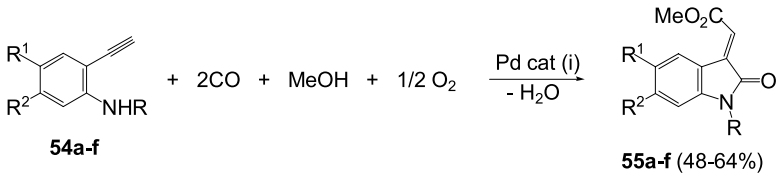
The palladium-catalysed reaction of the readily accessible 2-alkynyltrifluoroacetanilides with aryl halides and vinyl triflates under a carbon monoxide atmosphere (1 or 7 atm) in the presence of potassium carbonate produced the 2-substituted-3-acylindoles in fair to good yield. The acidity of the nitrogen–hydrogen bond proved to be of primary importance for the success of the reaction. This methodology has been applied to the synthesis of pravadole **53**, a drug that shows analgesic activity against postoperative pain. Pravadole **53** was prepared from the acylindole **52**, which was obtained by palladium-catalysed carbonylative cyclisaton of the alkynyltrifluoracetanilide **51** with *p*-iodanisole[39] (Scheme 20).



Scheme 19. (i) $PdCl_2(PPh_3)_2$ (1 mol%); CuI (2 mol%), NEt_3, MeCN; (ii) HO_2CCO_2H, MeOH, H_2O; (iii) $PdCl_2$, MeOH, $CuCl_2$, NaOAc, MeCN; (iv) (1) H_2, Pd–C, THF/HOAc (81% yield); (2) DIBAL, CH_2Cl_2 (61% yield); (3) MnO_2, EtOAc (87% yield).



Scheme 20.



Scheme 21. a R=R^1=R^2=H; **b** R=Bn, R^1=R^2=H; **c** R=Bu, R^1=R^2=H; **d** R=H, R^1=Me, R^2=H; **e** R=H, R^1=Cl, R^2=H; **f** R=R^1=H, R^2=Cl. (i) PdI_2 (2×10^{-3}–5×10^{-3} equiv.), KI (0.2–0.5 equiv.).

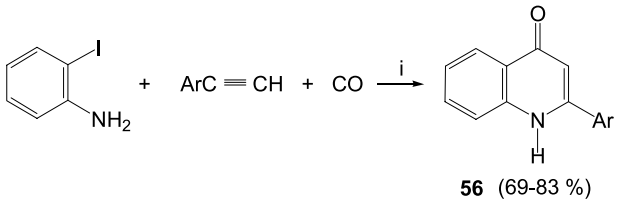
9. Synthesis of (*E*)-3-(methoxycarbonyl)methylene-1,3-dihydroindol-2-ones

Gabriele, et al. have reported a direct synthesis of (*E*)-3-(methoxycarbonyl)-methylene-1,3-dihydroindol-2-ones **55a-f** in good yields by the palladium-catalysed oxidative carbonylation of 2-ethynylanilines **54a-f**.[40] The reactions were carried out in MeOH as the solvent at 50–70 °C in the presence of catalytic amounts of PdI_2 in conjunction with KI under a 4:1 CO/air mixture (20 atm total pressure at 25 °C) (Scheme 21). The (*E*)-configuration around the double bond of **55a** was confirmed by a single crystal X-ray analysis.

The authors proposed that the formation of **55** could be interpreted by the formation of a carbamoylpalladium species, which then inserts into the triple bond. Another probable mechanism is the formation of an I–Pd–CO_2Me species by the reaction between PdI, CO and MeOH, followed by triple-bond insertion. In any event, however, the triple bond insertion is expected to be *syn*, to give vinylpalladium intermediates with (*Z*)-stereochemistry. Isomerisation of a (*Z*)-vinylpalladium intermediate into the corresponding (*E*)-isomer, followed by methoxycarbonylation, therefore appears to be the likely explanation for the stereoselective formation of the (*E*)-products **55**.

10. Synthesis of 2-aryl-4-quinolones

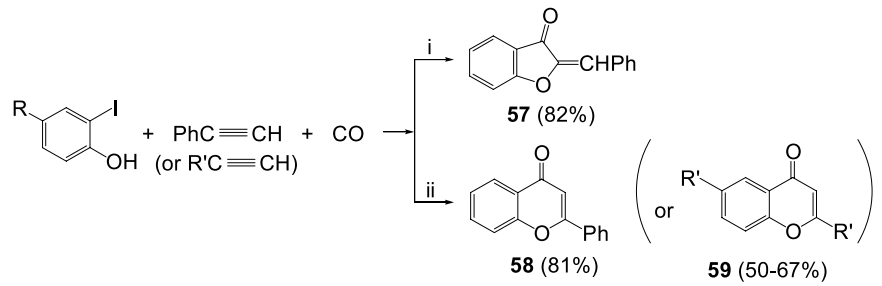
Kalinin et al. have shown that the carbonylation of *o*-iodoaniline and terminal arylacetylenes in the presence of palladium complexes leads to the 2-aryl-4-quinolones **56**.[41] The optimised reaction conditions with respect to pressure, amines, solvents and catalysts are listed in Scheme 22, the best catalyst being the $PdCl_2$(dppf) complex (dppf=1,1′-bis(diphenylphosphinoferrocene).

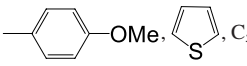


Scheme 22. (i) Et_2NH, 'Pd' cat, 120 °C, 20 atm, 1 h, Ar=Ph, C_6H_4OMe.

11. Synthesis of aurones and chromones

Carbonylation of *o*-iodophenol in the presence of phenylacetylene, potassium acetate and $Pd(PPh_3)_4$ in anisole at 1 atm CO leads to aurone **57** formation (Scheme 23).[42] When the reaction was carried out in the secondary amine

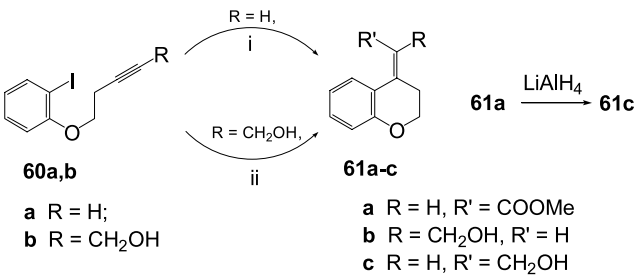


Scheme 23. (i) KOAc, $Pd(PPh_3)_4$, CO (1 atm), anisole; (ii) $PdCl_2$(dppf) (2 mol%), CO (20 atm), Et_2NH, 120°, 2 h R=H, R′=  , C_5H_{11}; R=Me, R′=Ph.

(the best was Et_2NH) at 20 atm CO and with catalysis by 2 mol% $PdCl_2$(dppf), the flavone **58** was formed (Scheme 23).[43] Selective formation of the aurone or flavone by carbonylation of *o*-iodophenol and phenylacetylene was achieved by manipulation of the reaction conditions (temperature, CO pressure) and the bases used. The influence of the nature of the solvent, amine, catalyst, CO pressure, and temperature on the yield of the flavone was studied.[43,44] The palladium-catalysed coupling of *o*-iodophenols proceeded either with aryl or heteroaryl halides and alkylacetylenes, giving the corresponding 2-substituted chromones **59** in good yield.[44]

12. Synthesis of (*E*)- and (*Z*)-substituted methylene-3,4-dihydro-2*H*-1-benzopyrans

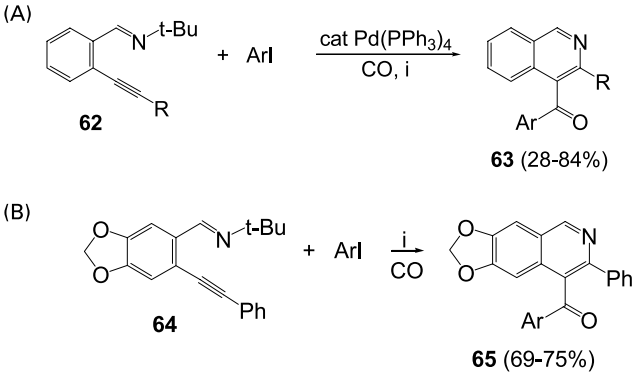
A stereoselective controlled synthetic approach to (*E*)- and (*Z*)-substituted methylene-3,4-dihydro-2*H*-1-benzopyrans **61a-c** was developed starting from the *o*-iodoalkynes **60a**,**b** through palladium-catalysed intramolecular cyclic carbopalladation of iodoalkynes **60**, followed by carbonylation or a hydride ion capture process (Scheme 24).[45] The influence of various solvents, catalysts and additives on the yields of the benzopyrans **61** was studied. The maximum yields obtained were 79% for benzopyran **61a** and 79% for benzopyran **61b**.



Scheme 24. (i) $Pd(PPh_3)_4$ (10 mol%), CO (1 atm), Et_3N (4 equiv.), AgOAc (3 equiv.) in MeOH–DMF–H_2O (1:1:0.2) at 100 °C; (ii) HCOONa (2 equiv.), Bu_4NCl (2 equiv.), $Pd(OAc)_2$ (10%), PPh_3 (20%) in DMF at 80 °C.

13. Synthesis of 3-substituted 4-aroylisoquinolines

Dai and Larock have shown that the *o*-(1-alkynyl)benzaldimines **62** and **64** react with aryl iodides at 1 atm of CO in the presence of tri-*n*-butylamine and $Pd(PPh_3)_4$ catalyst to afford in good yields the 3-substituted 4-aroylisoquinolines **63** or **65** by acylpalladation of the carbon–carbon triple bond and cyclisation (Scheme 25).[46,47]

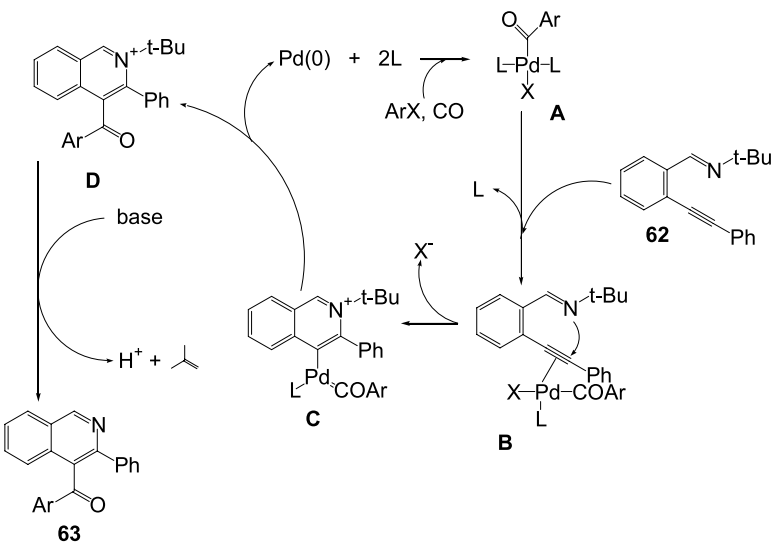


Scheme 25. (A): R=Ph, 1-cyclohexenyl, *n*-Bu, 3-cyanopropyl, *p*-$OMeC_6H_4$ Ar=*p*-(*m*- or *o*-)$MeOC_6H_4$,*p*-(*m*- or *o*-)MeC_6H_4, Ph, 1-naphthyl, 2-(3-)thienyl, *p*-BrC_6H_4, *m*-(*o*-)$EtO_2CC_6H_4$, *m*-(*p*-)$F_3CC_6H_4$, *p*-(*m*- or *o*-)$O_2NC_6H_4$. (B): Ar=*p*-$MeOC_6H_4$, *m*-$F_3CC_6H_4$ (i) DMF, $Pd(PPh_3)_4$ (4 mol%), Bu_3N (5 equiv.), 100 °C.

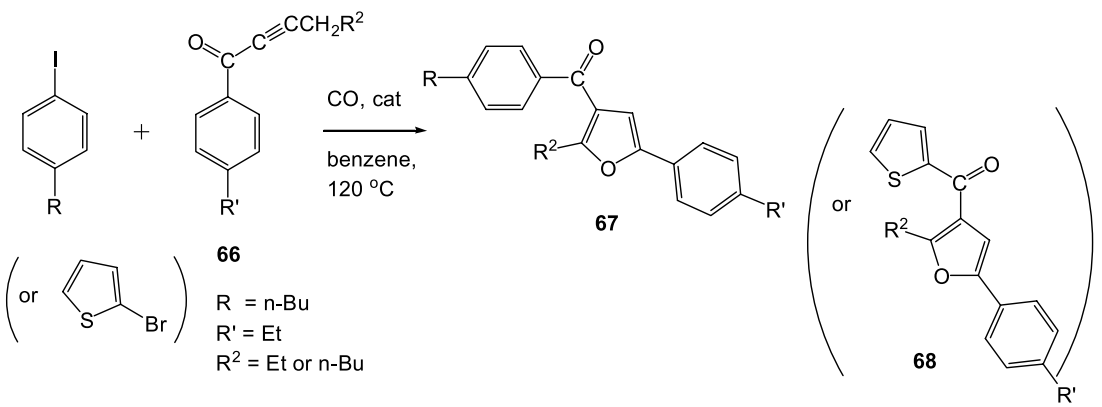
The authors proposed,[46,47] that the mechanism of this process (Scheme 26) includes the following key steps: (1) oxidative addition of the aryl halide to the Pd^0 catalyst, followed by CO insertion; (2) coordination of the resulting acylpalladium intermediate **A** to the alkyne triple bond of **62** to form the complex **B**, which activates the triple bond towards nucleophilic attack; (3) intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated carbon–carbon triple bond to afford the intermediate **C**; (4) reductive elimination to form a carbon–carbon bond between the carbonyl group and the isoquinoline ring in **D** and simultaneous regeneration of the Pd^0 catalyst; and (5) cleavage of the *tert*-butyl group from the nitrogen to release the strain between the *tert*-butyl group and the 3-phenyl group with simultaneous generation of the 3-substituted 4-aroylisoquinoline **63**.

14. Synthesis of substituted furans

2-Substituted-3-(4-substituted-benzoyl)-5-(4-substituted-phenyl)furans **67** were synthesised by palladium-catalysed cross-carbonylation of aryl iodides and 1-aryl-2-alkynyl-1-ones **66** with CO in benzene in the presence of $PdCl_2(PPh_3)_2$ at 120 °C (Scheme 27). In a similar manner, 2-substituted-3-thienoyl-4-substituted-phenyl)furans **68** were obtained from 2-bromothiophene and the arylalkynylketones **66**.[48]



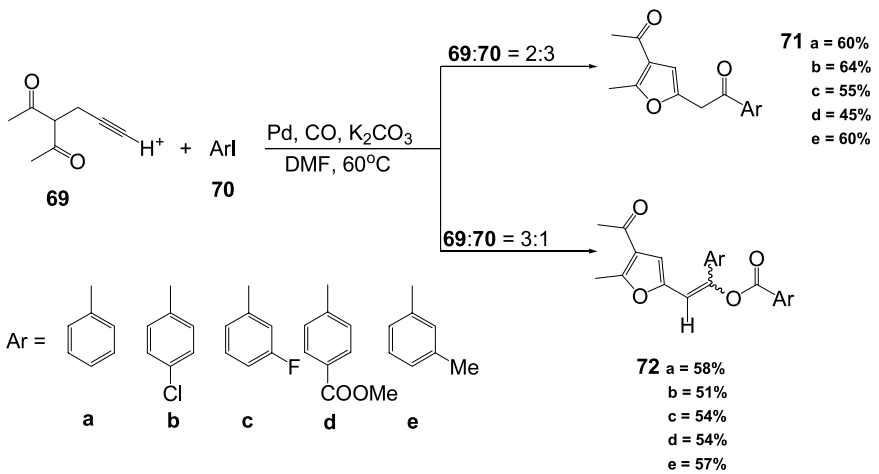
Scheme 26.



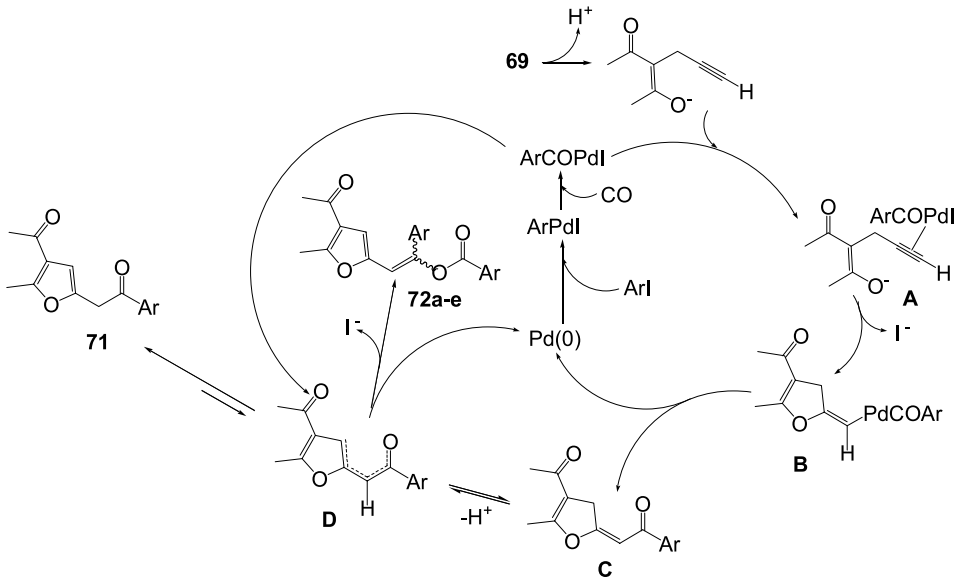
Scheme 27.

The palladium-catalysed reaction of 3-acetyl-5-hexyn-2-one with aryl iodides **70** under a CO atm produced different 2,3,5-trisubstituted furans **71**, and **72** depending on the alkyne/aryl iodide ratio (Scheme 28).[49]

An investigation of the influence of the catalysts, temperature and the **69**:**70** ratio on the reaction outcome has shown that palladium complexes with weakly coordinated ligands gave satisfactory results. The use of $Pd(OAc)_2/P(o\text{-tol})_3$, as a catalytic system, in acetonitrile, under a CO atmosphere at 60 °C and a **69**:**70** ratio of 2:3 enabled a chemoselective synthesis of **71**. Both $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$, in the absence of phosphine ligands, were also effective catalysts.



Scheme 28.



Scheme 29.

The authors proposed that the cyclisation of **69** can be rationalised according to the following sequence: (a) formation of the oxidative addition complex ArPdI between ArI and a Pd^0 species generated in situ; (b) carbonylation of ArPdI to give the σ-acylpalladium intermediate ArCOPdI; (c) generation of the π-alkynyl-palladium complex **A**; (d) generation of the σ-vinyl-palladium complex **B** via the regioselective *trans* addition of oxygen and palladium across the carbon–carbon triple bond (*exo*-dig process); and (e) reductive elimination of **C** to give Pd^0, followed by isomerisation of **C** to **71** (Scheme 29). Upon changing the **69**:**70** ratio from 2:3 to 3:1, further acylation of **D** was achieved by the capture of acylpalladium intermediates ArCOPdI furnishing the enol esters **72** as the sole product.[49]

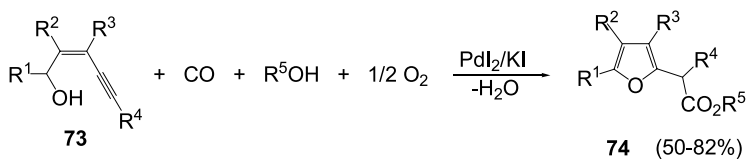
Gabriele et al. have shown that carbonylation of (*Z*)-2-en-4-yn-1-ols **73** under oxidative conditions gave the substituted furan-2-acetic acid esters **74** in good yields (Scheme 30). The cyclisation–alkoxycarbonylation process occurs in alcoholic media at 50–70 °C and under 100 atm pressure of a 9:1 mixture of CO and air in the presence of catalytic amounts of PdI_2 in conjunction with KI.[50]

The proposed reaction pathway involves the in situ isomerisation of the initially formed (*E*)-2-[(alkoxy-carbonyl)methylene]-2,5-dihydrofuran species **75** and **75a**, which in some cases have been isolated and proved to be the intermediates (Scheme 31).

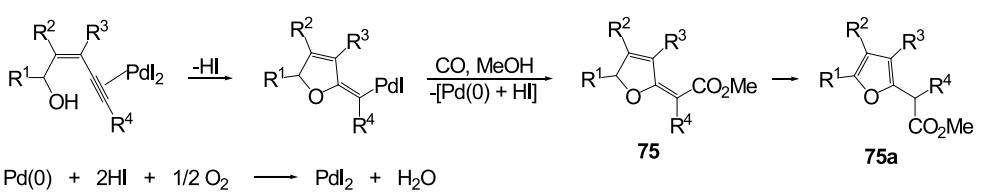
15. Synthesis of substituted pyrroles

Gabriele et al. have found recently that carbon dioxide effectively promotes the Pd-catalysed oxidative cyclisation–alkoxycarbonylation of (*Z*)-(2-en-4-ynyl)amines **76**, leading to the pyrrol-2-acetic acid esters **77** (Scheme 32).[51] In the absence of carbon dioxide, the yields of the pyrroles **77a**,**b** were lower (45 and 36% respectively) in addition to a mixture of the competitive cycloisomerisation products being formed.

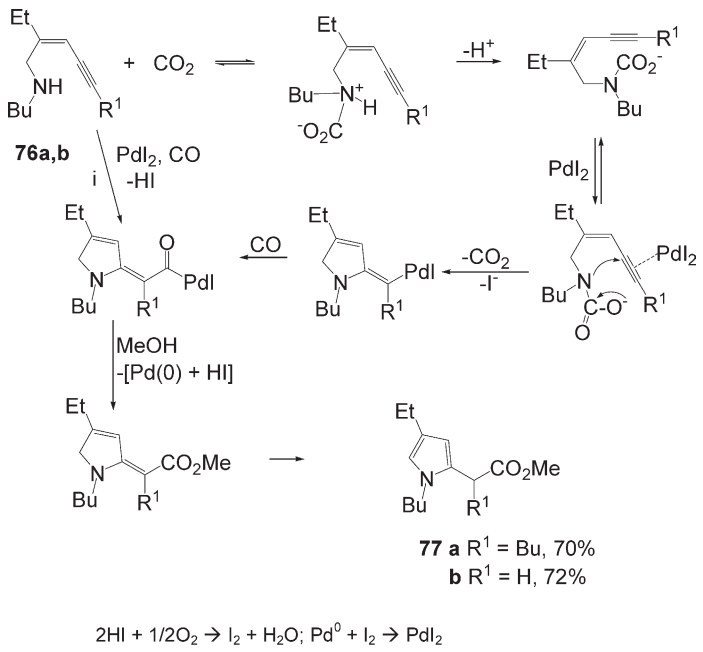
A convenient and general method for the formation of substituted pyrroles from an alkyne, an imine and carbon monoxide has been developed by Gao et al.,[52] who reported that the titanium–acetylene complexes **78**, which were generated in situ from the acetylenes, $Ti(OiPr)_4$ and *i*PrMgX



Scheme 30. R^1=H, Pr, Et, Ph; R^2=H, Et, Ph; R^3=H, Me, Et, Ph; R^4=H, Bu, Ph, TMS; R^5=Me, Bu.



Scheme 31.



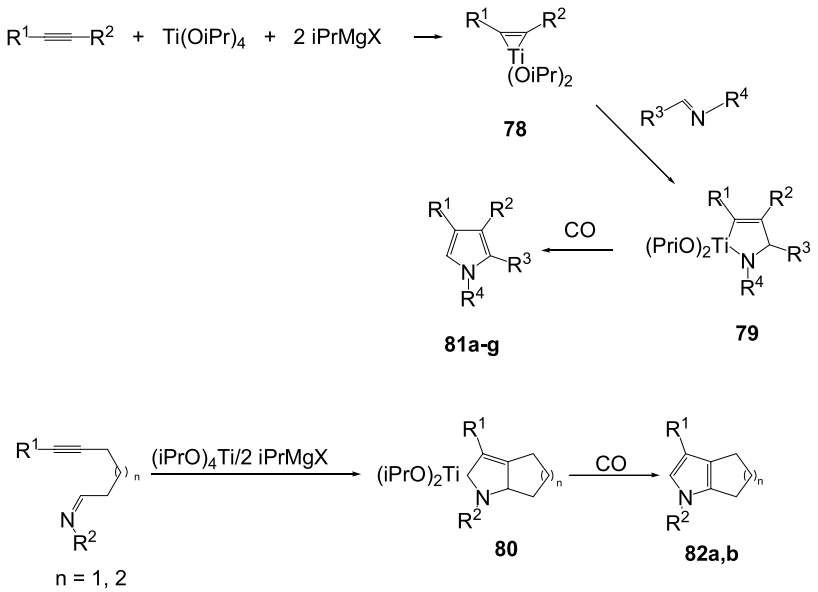
Scheme 32. (i) PdI_2:KI:**76** mol ratio=1:200:100, CO (30 atm), air (10 atm), CO_2 (50 atm), conc. −0.05 mmol/ml, MeOH, 70 °C, h.

(X=Cl or Br), react with imines to afford the azatitanacyclopentenes **79**. Similarly, bicyclic azatitanacyclopentenes **80** are formed from unsaturated imines, $Ti(OiPr)_4$ and *i*PrMgX (Scheme 33). Treatment of **79** and **80** with CO afforded the products **81** and **82**, respectively.

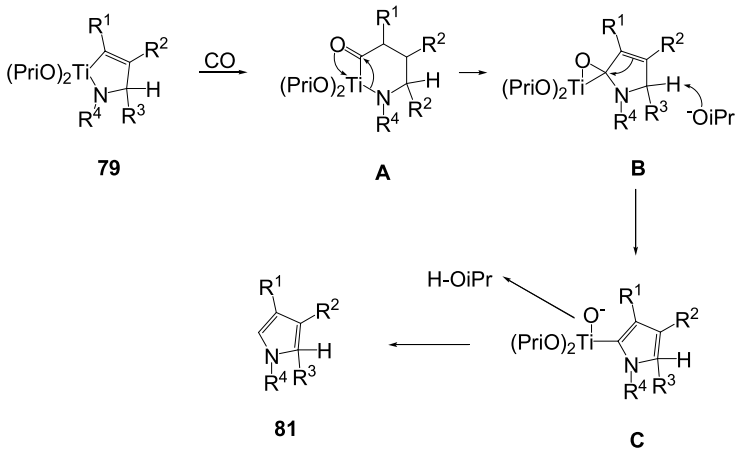
The authors proposed that insertion of CO into the Ti–C bond of **79** would produce the metallacyle **A**. Migration of the nitrogen atom from titanium to the acyl carbon would produce the titanium complex **B**. The intermediate **B** may undergo prototropic rearrangement induced by the *i*PrO anion (generated by the reaction of $Ti(OiPr)_4$ with *i*PrMgCl) to give **C** which affords the pyrrole **81** by alcoholysis with *i*PrOH produced in situ (Scheme 34).

16. Synthesis of 2*E*-[(methoxycarbonyl)methylene]tetrahydrofurans

4-Yn-1-ols **83a-d** bearing a terminal carbon–carbon triple bond undergo oxidative cycliation alkoxycarbonylation in methanol at 70 °C and 100 atm of a 9:1 mixture of CO/air in the presence of catalytic amounts of $[PdI_4]^{2-}$ in conjunction with an excess of KI to give the 2*E*-[(methoxycarbonyl) methylene]tetrahydrofurans **84a-d** in good yields, together



Scheme 33. 81: **a** R^1=R^2=R^4=Pr, R^3=Ph, (61%); **b** R^1=$SiMe_3$, R^2=C_6H_{13}, R^3=Ph, R^4=Pr, (71%); **c** R^1=$SiMe_3$, R^2=C_6H_{13}, R^3=Et, R^4=CH_2Ph, (74%); **d** R^1=$SiMe_3$, R^2=$(CH_2)_3OTBS$, R^3=Ph, R^4=Pr, (64%); **e** R^1=$SiMe_3$, R^2=$(CH_2)_3Br$, R^3=Ph, R^4=Pr, (63%); **f** R^1=$SiMe_3$, R^2=C_6H_{13}, R^3=$(CH_2)_3CH$, R^4=iPr, (67%); **g** R^1=$SiMe_3$, R^2=iPr, R^3=Ph, R^4=Pr, (76%). **82**: **a** R^1=$SiMe_3$, R^2=iPr, n=1 (84%); **b** R^1=$SiMe_3$, R^2=iPr, n=2 (82%).



Scheme 34.

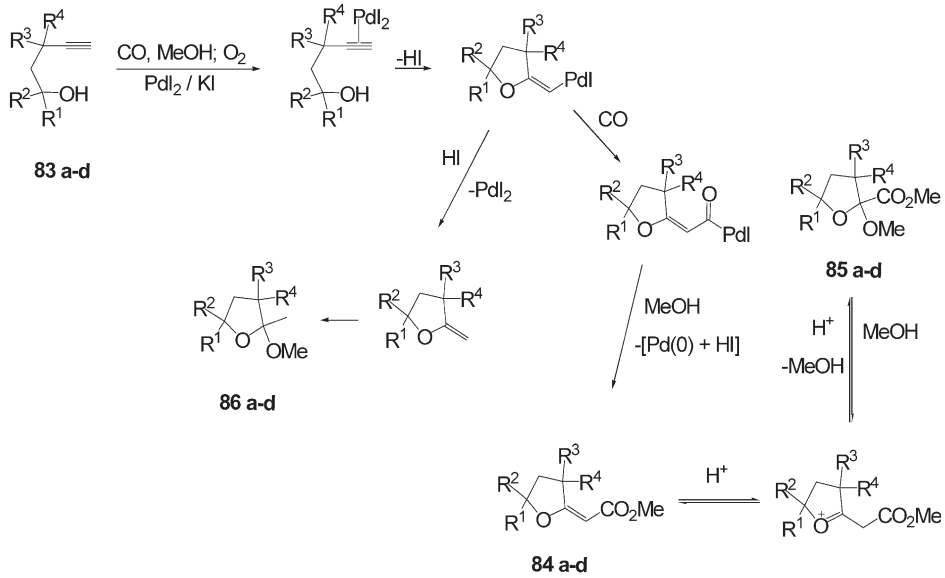
with the products **85**, which can be derived from methanol addition to the vinyl ethereal bond of **84**. A competing reaction, cyclic isomerisation and hydromethoxylation, leads to the 2-methoxy-2-methyltetrahydrofurans **86**, and this can be easily curtailed by increasing the KI excess. Alternatively, the latter products can be prepared from 4-yn-1-ols and MeOH in high yields using the same catalytic system and without a KI excess in the absence of CO (Scheme 35).[53]

Kato et al. presented the first example of asymmetric cyclisation–carbonylation of cyclic-2-methyl-2-propargyl-1,3-diols **87** catalysed by palladium(II) with chiral bisoxazolines. The reaction of **87** in the presence of palladium(II)-chiral ligands/*p*-benzoquinone in methanol at 0 to −40 °C under a carbon monoxide atmosphere (balloon) afforded the (*E*)-bicyclic-β-alkoxyacrylates **88** (Scheme 36) in excellent yields with moderate enantioselectivities.[54]

The oxidative cyclisation carbonylation of 4-yn-1-ones **89** in the presence of $(MeCN)_2PdCl_2$/*p*-benzoquinone in methanol under a CO atmosphere (balloon) afforded the 5-methoxy-2*E*-[(methoxycarbonyl)methylene]tetrahydrofurans **90** (Scheme 37).[55] The products **90** can be easily converted into the 2-cyclopentenone carboxylates **91**.

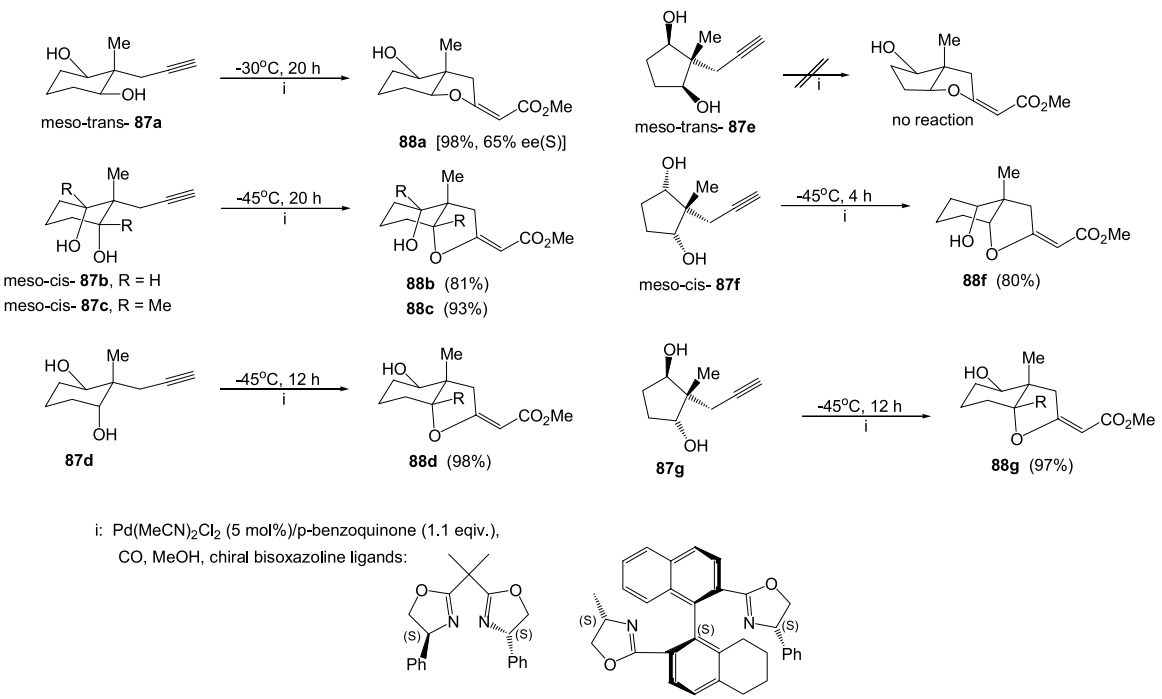
A conceivable mechanism of the reaction may be proposed as shown in Scheme 38 on the basis of the experimental results.

Recently, Kato et al. reported the first example of asymmetric cyclisation–carbonylation of the 2-propargyl-1,3-diones **92** and **94** into the substituted 2*E*-[alkoxycarbonyl)methylene]tetrahydrofurans **93** or **95**, the reaction

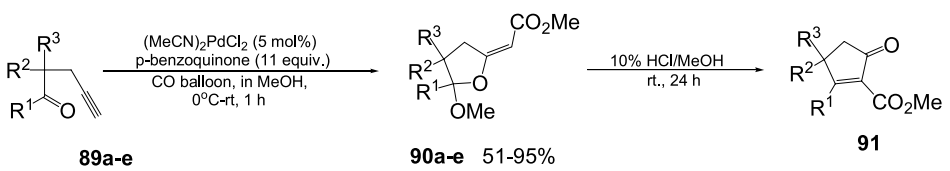


$$Pd(0) + 2HI + 1/2\ O_2 \rightarrow PdI_2 + H_2O$$

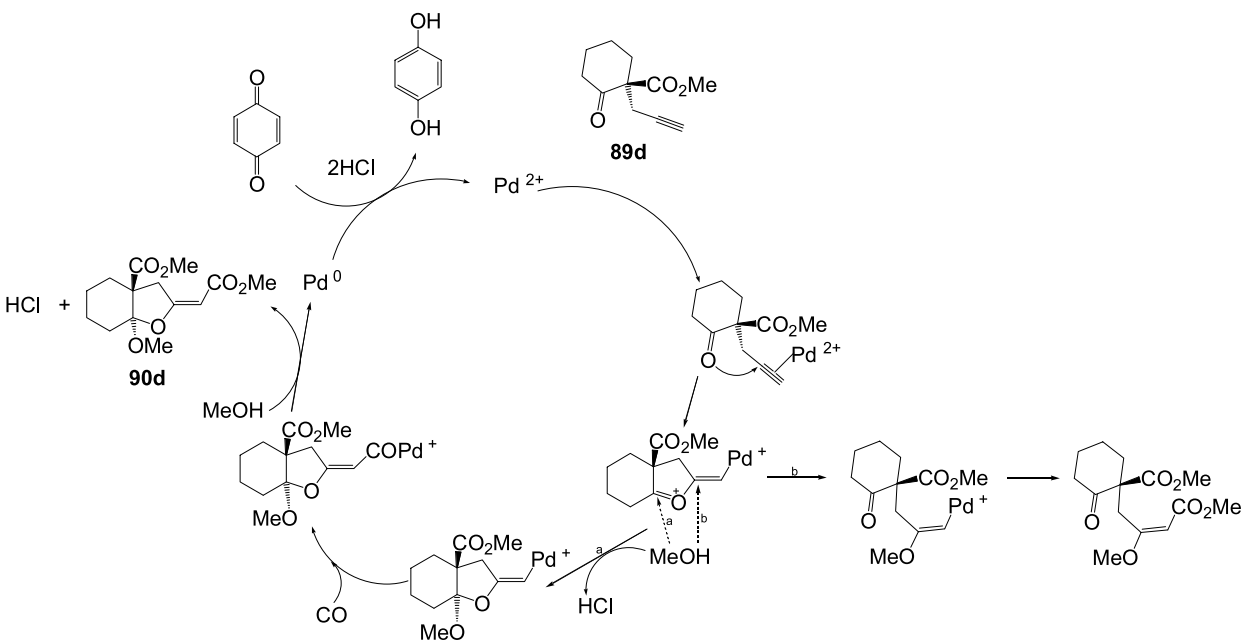
Scheme 35. a $R^1{=}R^2{=}R^3{=}R^4{=}H$, **84** 24%, **85** 40%, **86** 15%. **b** $R^1{=}Me$, $R^2{=}R^3{=}R^4{=}H$, **84** 32%, **85** 45%, **86** 16%. **c** $R^1{=}R^2{=}Me$, $R^3{=}R^4{=}H$, **84** 41%, **85** 37%, **86** 13%. **d** $R^1{=}R^2{=}H$, $R^3{=}R^4{=}Me$, **84** 29%, **85** 19%, **86** 20%.



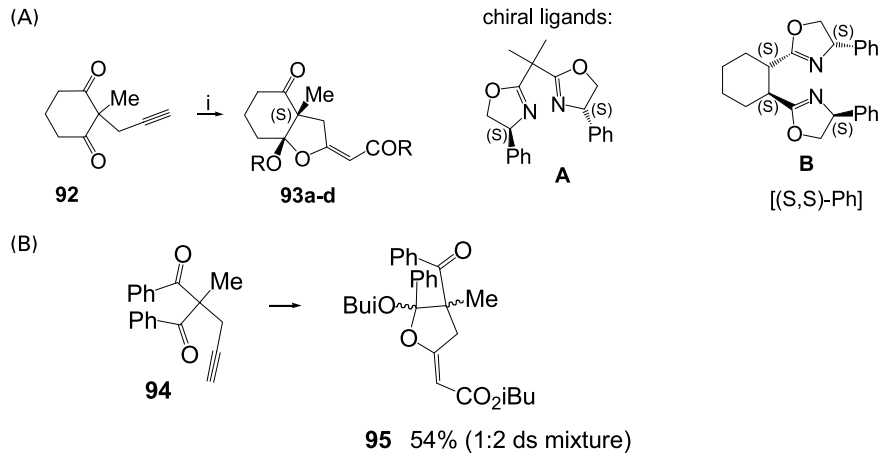
Scheme 36.



Scheme 37. 88: **a** R^1=R^3=Me, R^2=CO_{23}Me, (82%); **b** R^1=Me, R^2=CO_2Me, R^3=H (51%); **c** R^1=$(CH_2)_3CO_2$Me, R^2=Me, R^3=H, (95%); **d** R^1 R^2=$(CH_2)_4$, R^3=CO_2Me (64%); **e** R^1 R^2=$(CH_2)_4$, R^3=CO_2Et (70%).



Scheme 38.



Scheme 39. (A) (i) $Pd(CF_3CO_2)_2$ (5 mol%), chiral ligand (5 mol%); *p*-benzoquinone (1.1 equiv.), CO, ROH (solvent). **93**: **a** R=Me, yield 90%, ee 8% (*R*) with ligand A; **b** R=*i*Pr, yield 54%, ee 33% (*S*) with ligand A; **c** R=Bu, yield 62%, ee 27% (*S*) with ligand A; **d** R=*i*Bu, yield 48%, ee 43% (*S*) with ligand A; yield 54%, ee 59% (*R*) with ligand B. (B) (i) $Pd(CO_2CF_3)_2$ (5 mol%), ligand A (5 mol%), CO, *i*BuOH, 0 °C, 48 h.

being catalysed by palladium(II) with chiral bisoxazolines. The use of the chiral bisoxazolines **A** and **B** has given the best enantioselectivity among all of the investigated chiral ligands[56] (Scheme 39).

17. Unusual formation of cyclic orthoesters

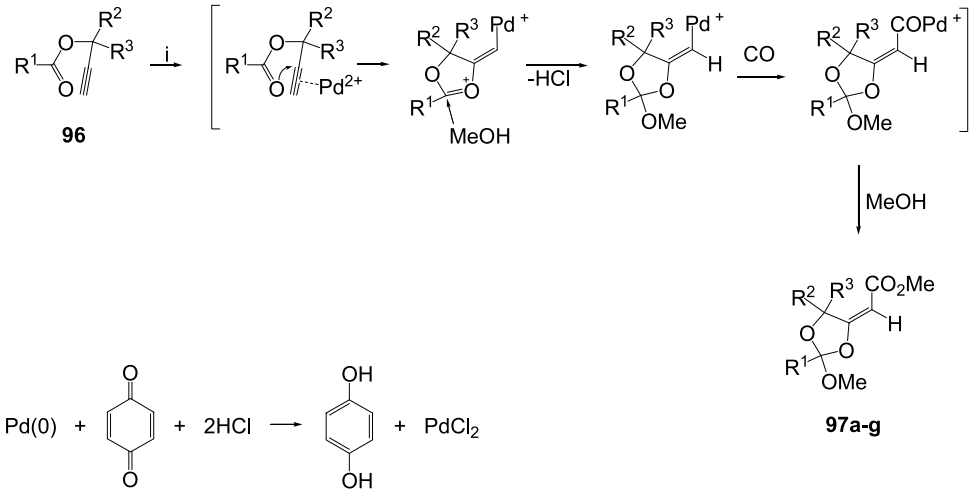
Kato et al. reported the oxidative cyclisation methoxycarbonylation of the propargylic acetates **96** in the presence of $(MeCN)_2PdCl_2$/*p*-benzoquinone in methanol under CO atmosphere which afforded the (*E*)-cyclic-orthoesters **97** in moderate yields (Scheme 40).[57]

18. Facile stereoselective synthesis of oxathiolanes

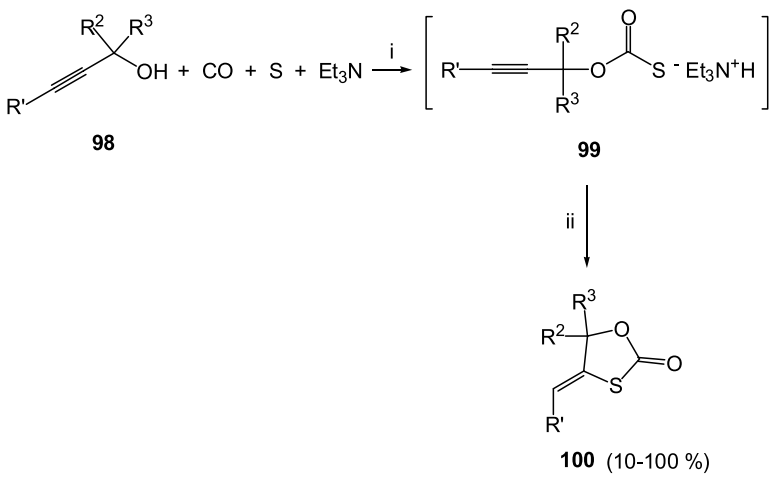
The stereoselective interaction of alkynols **98** with elemental sulphur, carbon monoxide and triethylamine offers the salts **99**. The latter salt can be cyclised into 4-alkylidene-2-oxo-1,3-oxathiolanes **100** under catalytic conditions (Scheme 41). CuI was shown to have the best activity among the various studied catalysts (CuCl, $CuCl_2$, CuBr, $CuBr_2$, CuI, $CuSO_4$, $FeCl_2.4H_2O$, $FeCl_3$, $CoCl_2$, $CoBr_2$, CoI_2, $NiCl_2$, $ZnCl_2$, $ZnBr_2$, ZnI_2 and $PdCl_2$).[58]

19. Stereoselective synthesis of selenium-containing heterocycles

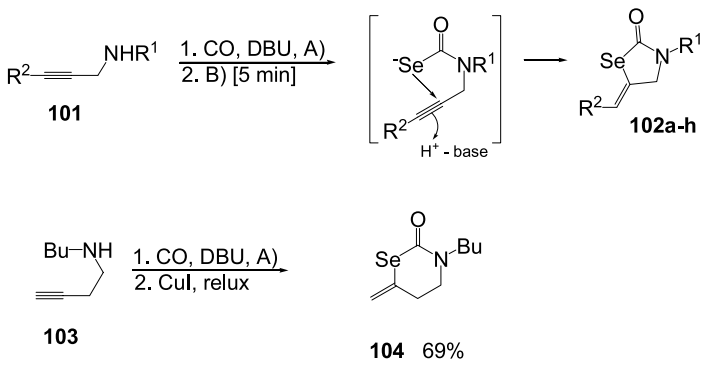
Carbonylation of the aminoalkynes **101** and **103** with carbon monoxide in the presence of selenium provides access towards carbamoselenoate intermediates, which subsequently undergo intramolecular cycloaddition to furnish the corresponding alkylideneselenazolinones **102** and **104**. The reaction of the internal aminoalkynes **101g**, and **101h** afforded the products **102g**, and **102h** as the *Z*-isomers exclusively (Scheme 42).[59]



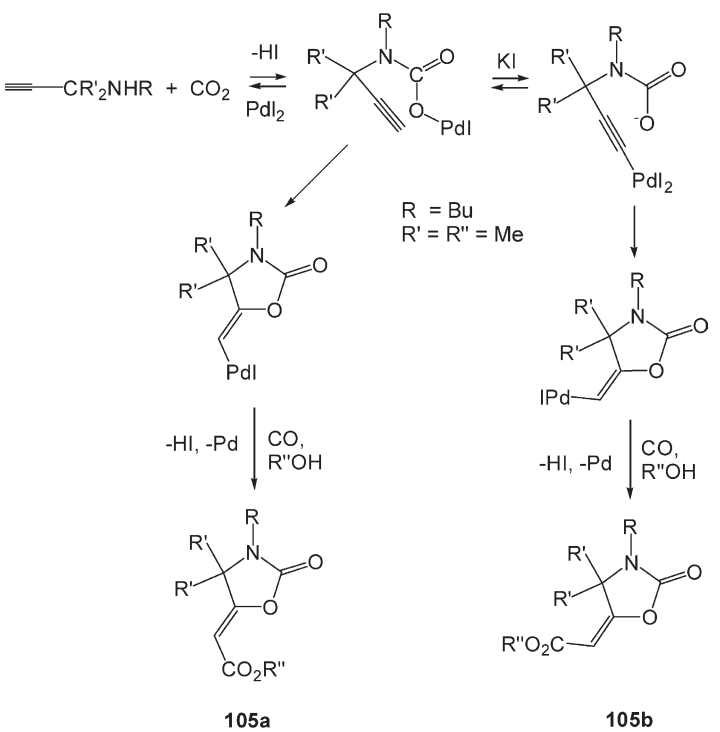
Scheme 40. (i) $(MeCN)_2PdCl_2$(5 mol%), p-benzoquinone (1.1 equiv.), CO (balloon), MeOH, 0 °C or rt. 0.5–7.0 h. **97**: **a** R^1=Me, R^2 R^3=$(CH_2)_5$, yields 65%; **b** R^1=Me, R^2 R^3=$(CH_2)_6$, yield 65%; **c** R^1=Me, R^2=Me, R^3=CH_2Bn, yield 61% (as a 2:1 diastereomeric mixture); **d** R^1=Me, R^2 R^3=$(CH_2)_2$-N(BOC)-$(CH_2)_2$, yield 71%; **e** R^1=Ph, R^2 R^3=$(CH_2)_5$, yield 80%; **f** R^1=*p*-NO_2Ph, R^2 R^3=$(CH_2)_5$, yield 21%; **g** R^1=*p*-MeOPh, R^2 R^3=$(CH_2)_5$, yield 83%.



Scheme 41. (i) THF, 30 atm, 80 °C, 4 h; (ii) CuI, rt, 18 h R′, R^2, R^3=H, Me, Et, CH_2OH, Ph.

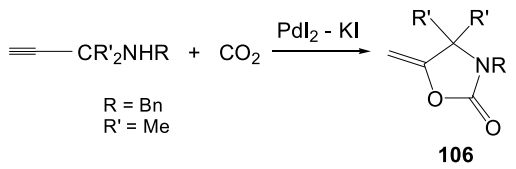


Scheme 42. 102: R^2=H; **a** R^1=Bu, 95%; **b** R^1=i-Pr, 56%; **c** R^1=Cy, 76%; **d** R^1=t-Bu, 10%; **e** R^1=Ph, 0%; **f** R^1=H, 0%; **g** R^1=Bu, R^2=Et, 68%; **h** R^1=Bu, R^2=$SiMe_3$, 22%. (A) 0.8 equiv. Se, THF, 25 °C, 1 atm [1.5 h]; (B) conc. aq. NH_4Cl, 25 °C.



$$2HI + {}^1/_2O_2 \rightarrow H_2O + I_2; \quad Pd + I_2 \rightarrow PdI_2$$

Scheme 43.



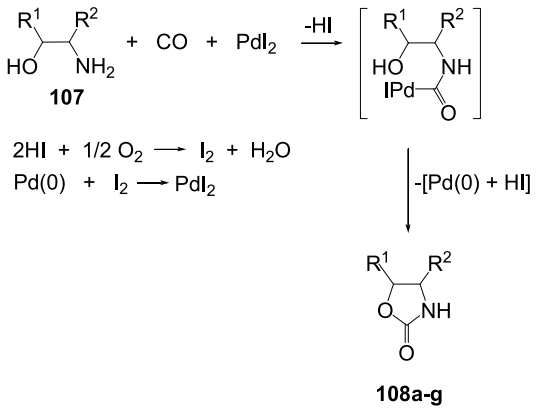
Scheme 44.

20. Oxazolidin-2-ones synthesis

Chiusoli et al. have shown for the first time that upon simultaneous interaction of the propargyl-alkylamines with carbon monoxide and a carbon dioxide catalysed by PdI_2 or Pd^0/C in the presence of KI, sequential carboxylation and alkoxycarbonylation reactions proceed, leading to the (*Z*)- and (*E*)-[(alkoxycarbonyl)methylene]oxazolidin-2-ones **105a** and **105b**[60,61] (Scheme 43).

In the absence of carbon monoxide, only the oxazolidinone **106** was formed (Scheme 44).

Recently, the same authors have shown that the 2-oxazolidinones **108** are obtained in excellent yields (up to 100%) with unprecedented catalytic efficiencies (up to 2000 mol product/mol of used catalyst) by the direct PdI_2/KI-catalysed oxidative carbonylation of the readily available 2-amino-1-alkanols **107** (Scheme 45). The reactions are carried out in MeOH as the solvent at 100 °C using a 1:6:5 $CO:O_2$:air mixture (60 atm total pressure at 25 °C).[62] The authors believe that a large excess of iodide anion and oxygen are primarily required to ensure a fast re-oxidation of Pd^0, according to Scheme 45.



Scheme 45. 108: **a** R^1=R^2=H, 90%; **b** R^1=Me, R^2=H, 100%; **c** R^1=Ph, R^2=H, 87%; **d** R^1=H, R^2=Me, 93%; **e** R^1=H, R^2=Ph, 98%; **f** R^1=H, R^2=Me_2CH, 100%; **g** R^1=H, R^2=$PhCH_2$, 86%.

21. Formation of substituted lactams

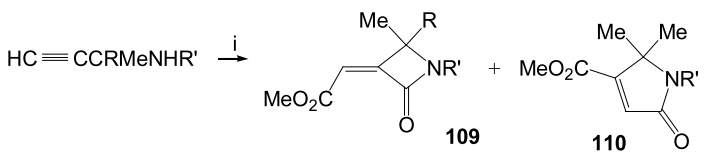
α-Methylene-β-lactams **109** are formed by carbonylation of α,α-disubstituted propargyl-alkylamines and γ-lactams **110** are formed from unsubstituted or acylated amines[63] (Scheme 46).

Mori and Ochifuji have developed a protocol for synthesizing the lactams **112-115** using the alkynes **111a-f** having an amide function in the molecules.[64] The reaction proceeds via a vinylketene complex **A**, generated from the alkyne and the Fisher chromium carbene complex, and the lactam ring was formed from carbon monoxide, alkyne, and the tosylamide nitrogen atom. The four-, five-, six-, and seven-membered lactams **112a-d** having a substituent at the α-position were obtained in good yields (Scheme 47).

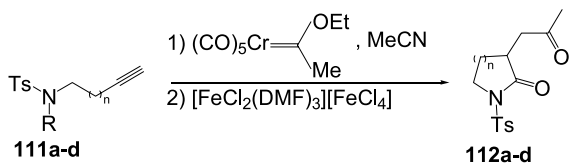
The cyclocarbonylation of the 1,6- and 1,7-yne-imines **116a-e** to the bicyclic α,β-unsaturated lactams **117a-e** can be achieved in the presence of a catalytic amount of $Ru_3(CO)_{12}$ (Scheme 48). The reaction, a [2+2+1] cycloaddition, incorporates the acetylene π-bond, and the carbon atom of CO. The presence of substituents, such as alkyl, aryl, and silyl on the acetylenic terminal carbon is essential for the yne-imines to undergo cyclocarbonylation to give the bicyclic α,β-unsaturated lactams. The absence of substituents on the acetylenic terminal carbon does not offer the corresponding lactam, but rather a dihydropyridine derivative without the incorporation of CO.[65]

Alper and Van den Hoven have shown[66] that the tandem cyclohydrocarbonylation/CO insertion of the α-iminoalkynes **118a-o** requires CO, H_2 and catalytic quantities of the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)Rh^+(1,5-cod) with triphenyl phosphite in order to gain the aldehyde-substituted pyrrolinones **119a-e** or **120f-o** in 67–82% yields. This transformation is readily applied to iminoalkynes containing alkyl, alkoxyl, vinyl, and aryl substituents (Scheme 49) and gives an attractive route to prepare highly functionalised pyrrolinones, which are important and versatile pharmaceutical. The authors discussed the postulated mechanism of **119** formation, which includes the generation of the active rhodium complex $HRhL_x$ binding to the acetylenic imine **118** via the triple bond and the imine, followed by intramolecular hydrorhodiation, and subsequent carbonylation cyclisation with a second CO insertion ended by hydration.

Alcaide et al. have found that the [2+2+1] carbonylative cyclisation of 2-azetidinone tethered allenynes **121** lead to the fused tricyclic β-lactams **123** bearing a central seven-membered ring as a single isomer. The cycloadducts **123** presumably arise from the isomerisation of the initially formed adducts **122** (Scheme 50). Conjugation of the

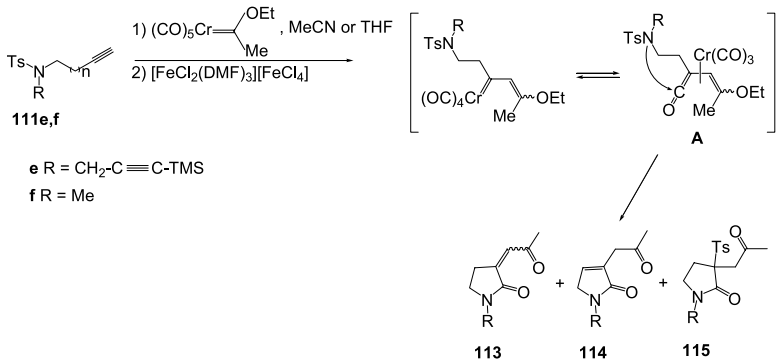


Scheme 46. R=Me, Et; R′=CH_2Ph, Alk, H, CH_2Alk. (i) CO/air, Pd^0/C, KI, MeOH.



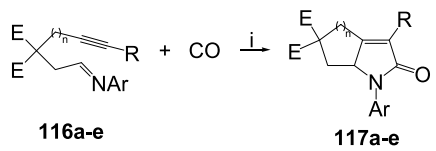
a R = H, $SiMe_3$, n = 0
b R = H, $SiMe_3$, n = 1
c R = H, n = 2
d R = H, n = 3

a n = 0, R = H (16%), R = $SiMe_3$ (50%)
b n = 1, R = H or $SiMe_3$ (85%)
c n = 2, R = H (82%)
d n = 3, R = H (84%)



R = CHC≡CTMS	22%	21%	0
R = Me	17%	0	13%

Scheme 47.



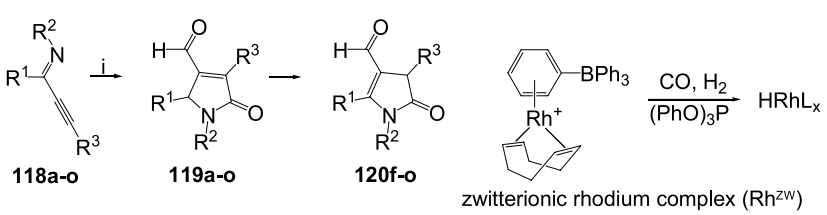
Scheme 48. 116, **117**: E=COOEt; Ar=*p*-$MeOC_6H_4$. **117 a** R=$SiMe_3$, n=1 (66%); **b** R=Ph, n=1 (45%); **c** R=Et, n=1 (43%); **d** R=$(CH_2)_2OBn$, n=1 (43%); **e** R=$SiMe_3$, n=2 (51%). (i) $Ru_3(CO)_{12}$ (5 mol%), toluene, CO (5 atm), 160 °C, 20 h.

dienone moiety with the lone pair of the nitrogen atom is believed to promote the formation of the compound **123**.[67]

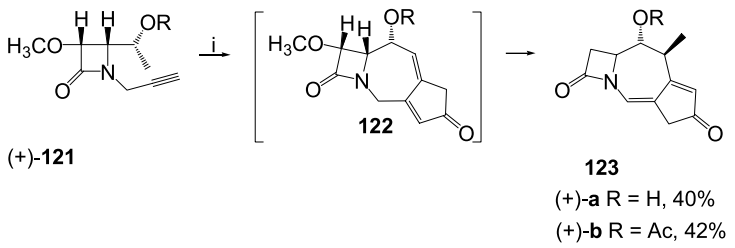
22. Synthesis of 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones

Van den Hoven and Alper have reported the cyclohydrocarbonylative ring expansion of the acetylenic thiazoles **124** in the presence of CO, H_2, catalytic quantites of the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)Rh^+(1,5-cod) and triphenyl phosphite to furnish the 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones **125** in 61–90% yields.[68] Thiazepinones are pharmacologically important compounds for the treatment of cancer, heart and inflammatory diseases. This novel transformation of a five- to a seven-membered heterocycle is readily applied to acetylenic thiazoles containing hydro, alkyl, alkyl halide, vinyl, and benzo substituents in positions 4 and 5 of the thiazole ring, in addition to alkyl-, ether-, ester-, vinyl- and aryl-substituted alkynes at position 2 (Scheme 51).

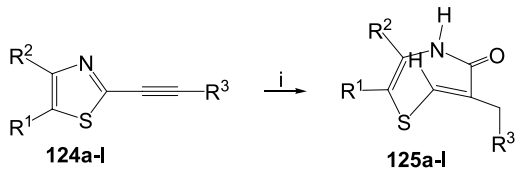
The authors propose a possible mechanism for the conversion of the acetylenic thiazoles **124** to the thiazepin-5-ones **125** (Scheme 52). The active rhodium complex $HPhL_x$, formed from the (η^6-$C_6H_5BPh_3$)Rh^+(1.5-cod)



Scheme 49. (i) Rh^{ZW} (2 mol%), $(PhO)_3P$ (8 mol%), CH_2Cl_2, CO/H_2 (21–42 atm), 75–100 °C, 18–36 h. **119a-e** R^1=Me, R^3=Et; **a** R^2=*n*-Bu (82%); **b** R^2=*i*Pr, (79%); **c** R^2=Cy (80%); **d** R^2=$CH_2[CHO(CH_2)_3]$ (73%); **e** R^2=$(CH_2)_2Ph$, (75%). **119**, **120f-j** R^1=Ph, R^2=*n*-Bu; **f** R^3=*n*-Bu, (78%); **g** R^3=Me, (72%); **h** R^3=[=$C(CH_3)_2$] (67%); **i** R^3=*i*-Pr; **j** R^3=CH_2–Cy (79%). **119**, **120k-o** R^2=*i*Pr; R^3=*n*-Bu; **k** R^1=Ph (80%); **e** R^1=*p*-MeC_6H_4 (81%); **m** R^1=*p*-MeC_6H_4 (78%); **n** R^1=*p*-ClC_6H_4 (72%); **o** R^1=β-napth (75%).

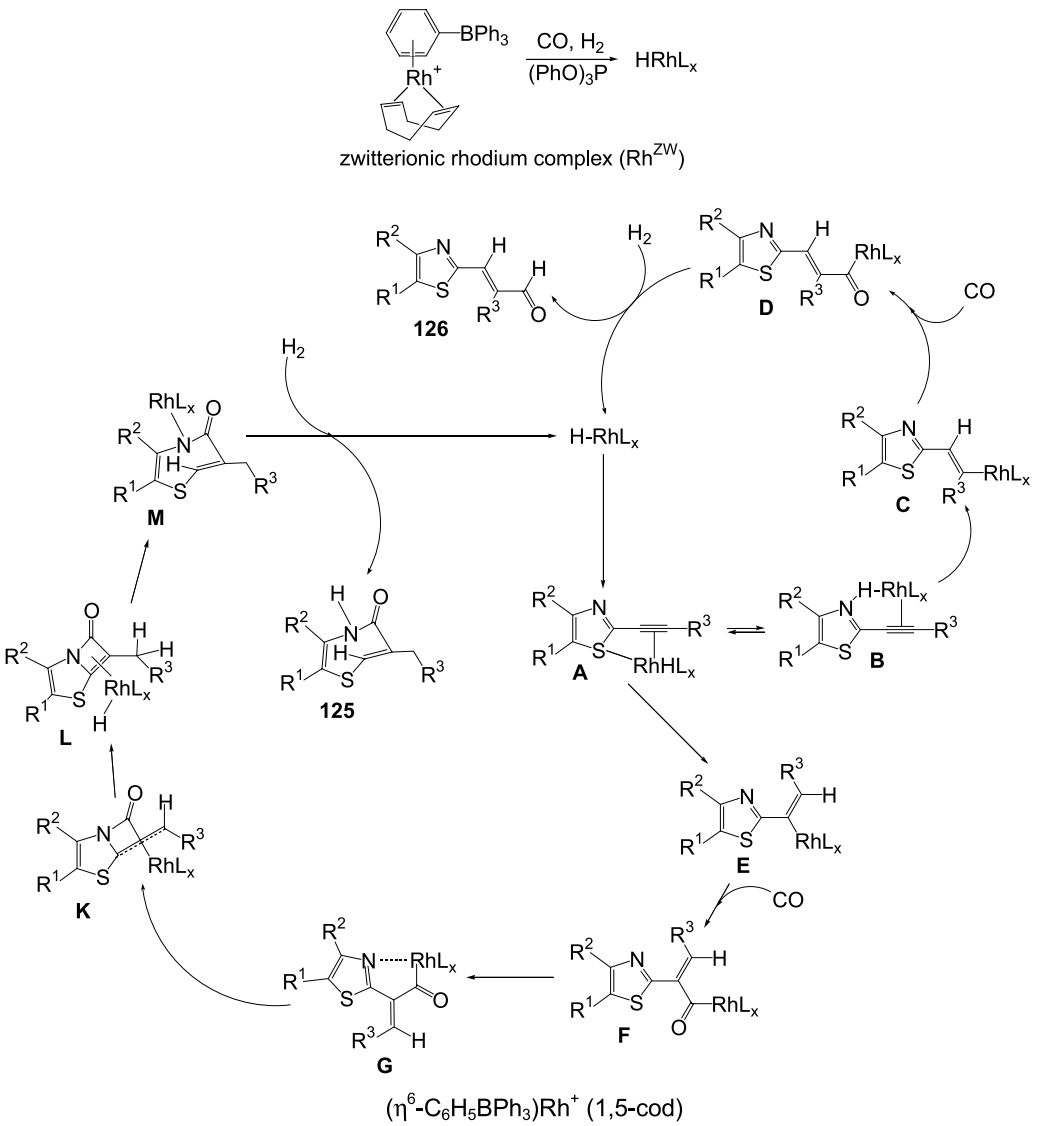


Scheme 50. (i) CO, $Co_2(CO)_8$ (1.1 equiv.), Me_3NO (2 equiv.), CH_2Cl_2, rt.

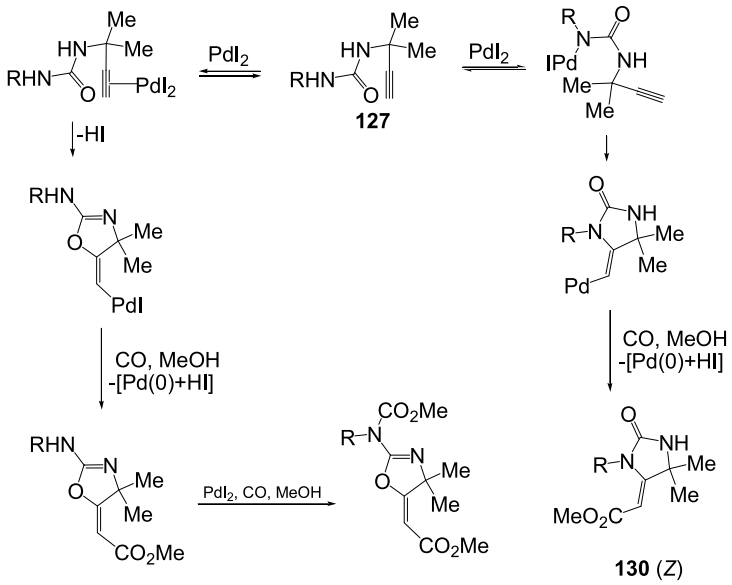


Scheme 51. (i) Rh^{ZW} (2 mol%), $(PhO)_3P$ (8 mol%), 21 CO/H_2 (1:1, 21 atm), CH_2Cl_2, 110 °C, 18–36 h. **125a-g** R^1=R^2=H; **a** R^3=*n*-Bu (86%); **b** R^3=*t*-Bu (89%); **c** R^3=Ph (90%); **d** R^3=*n*-MeC_6H_4 (87%); **e** R^3=*i*-Pr (72%); **f** R^3=CH_2OMe (74%); **g** R^3=$CH_2OC(O)Me$ (61%). **125h-l** R^3=*n*-Bu; **h** R^1=H, R^2=Me (83%); **i** R^1=R^2=Me (78%); **j** R^1=$(CH_2)_2Cl$, R^2=Me (78%); **k** R^1=CH(Me)C(O)H, R^2=Me, (81%); **l** R^1R^2=$(CH)_4$, (76%).

complex, binds to the thiazolyne **124** via the triple bond and a heteroatom (**A**) or possibly by H-bonding to the thiazole ring (**B**). Depending on the equilibrium between **A** and **B** two products may result. If **B** is favoured, subsequentent intramolecular insertion of the H–Rh bond into the alkyne would generate **C**. Carbonylation of the latter and subsequent addition of hydrogen to **D** would give the hydroformylation product **126**. On the other hand, if **A** is favoured, the intramolecular hydroformylation would proceed in the opposite manner to form **E**, carbonylation of which would give **F** and coordination with the heterocyclic nitrogen could then afford **G**. The intermediate



Scheme 52.



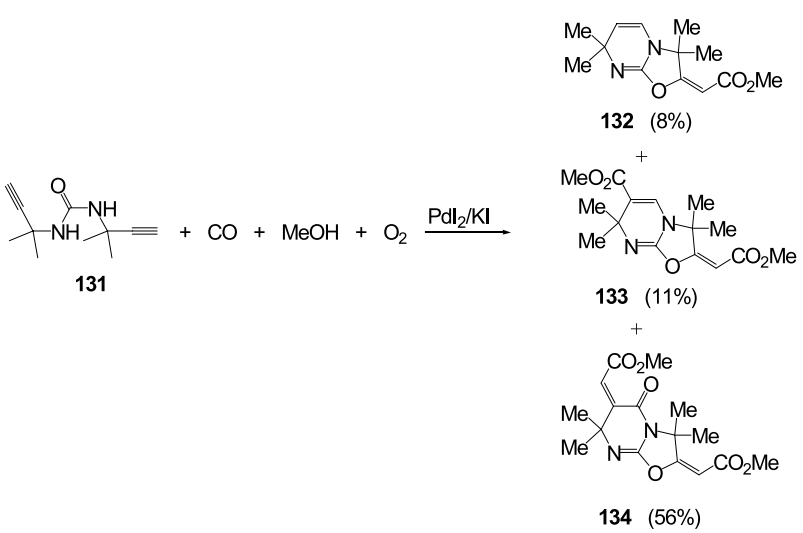
127		128 (%)	129 (%)	130 (%)
a	R = Pr	**a** 70	3	23
b	R = CH_2Ph	**b** 33	-	53
c	R = Ph	**c** 34	33	7
d	R = p-MeC_6H_4	**d** 47	-	35
e	R = H	**e** -	28	46

Scheme 53.

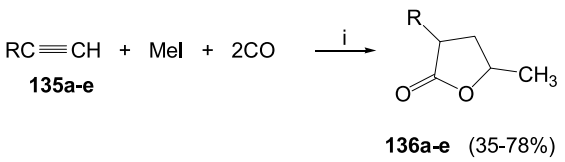
G can undergo intramolecular cyclisation, resulting in the formation of a β-lactam with allyl-type bonding to Rh (**K**). Hydrogen addition to **K** may afford a strained azetidinone-Rh hydride **L**. Hydrogen transfer with ring opening would form **M** as the *E*-isomer, with nitrogen coordinated to the rhodium. Addition of hydrogen completes the thiazepinone ring **125** and regenerates the rhodium complex $HRhL_x$.

23. Heterocycles from acetylenic ureas

Chiusoli et al. have shown that acetylenic ureas **127** readily undergo oxidative cyclisation–alkoxycarbonylation reactions in the presence of PdI_2- (or Pd/C)–KI as a catalyst in methanol under mild conditions (65 °C and 24 bar of a 3:1 mixture of CO and air).[69] Cyclisation occurs by *trans*-attack of oxygen or *cis*-attack of nitrogen functions on the triple



Scheme 54.



Scheme 55. a R=Ph, **b** R=$(CH_2)_2$Ph, **c** R=Bu, **d** R=Hex, **e** R=p-MeC_6H_4. (i) $Mn(CO)_5Br$ (1 equiv.), 5 N NaOH, CH_2Cl_2, $[PhCH_2NEt_3]^+Cl^-$-, 35 °C, CO (1 atm).

bond, followed by stereospecific carbonylation, resulting in (*E*)-**128**, (*E*)-**129** or (*Z*)-**130**, respectively (Scheme 53).

In the case of cyclisation–alkoxycarbonylation of the diacetylenic ureas **131**, condensed ring **132**-**134** formation occurs (Scheme 54). The structure of the main product **134** was determined by X-ray diffraction. It contains an (*E*)- and a (*Z*)-(methoxycarbonyl)methylene chain which were bonded to the condensed oxazoline and pyrimidinone rings, respectively.[69]

24. Synthesis of lactones

The alkynes **135a-e** react with methyl iodide, bromopentacarbonylmanganese (or dimanganese decacarbonyl), and carbon monoxide under phase-transfer catalysis conditions to give the 2,4-disubstituted γ-butyrolactones **136a-e**. The reaction conditions are mild (35 °C, 1 atm), and the process is regiospecific (Scheme 55).[70]

The α-substituted lactones **139** can be formed in a one-pot reaction of the alkynes **137** bearing a hydroxyl or silyloxyl group with the Fischer chromium carbene complex **138**. The reaction proceeds in a highly stereoselective manner (Scheme 56), and the desired monocyclic and bicyclic lactones **139** were obtained in good yields (Table 4).[71]

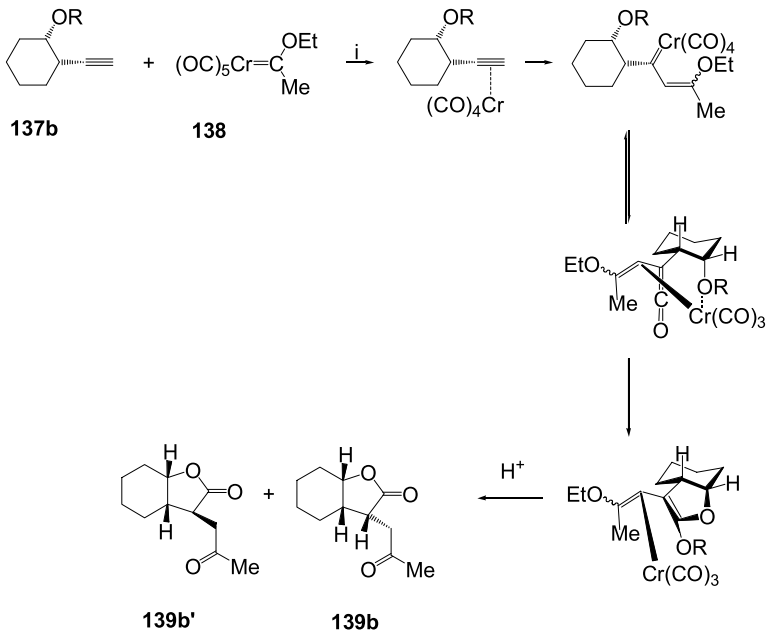
When the carbonylation of 5-hydroxy-1-pentyne was carried out in the presence of benzenethiol and $Pt(PPh_3)_4$ (3 mol%) under 3 atm of CO at 120 °C for 4 h, the cyclocarbonylation took place successfully to attain α[(phenylthio)methyl]-δ-lactone **140** selectively in a high yield (Scheme 57).[72]

25. α-Methylene-γ- and -δ-lactone synthesis

Novel synthetic methods for α-methylene-γ-butyrolactones are of interest owing to the high biological activity of these compounds and the wide spectrum of physiological action of natural products containing an α-methylenelactonic unit, for example, elephantopin, euparotin acetate and vernolepin, which show antitumor activity,[73] and the natural sesquiterpene lactone, phantomolin, which shows cytotoxic activity.[74] The method for catalytic cyclocarbonylation of acetylene alcohols is not compatible with the other methods and is not of great interest, owing to the low yields of α-methylene-γ-butyrolactones such as **141**, which was attained by reacting 3-butyn-1-ol with stoichiometric amount of nickel tetracarbonyl[75] (Scheme 58).

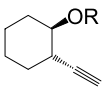
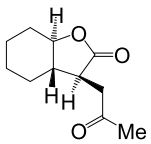
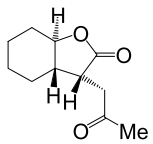
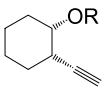
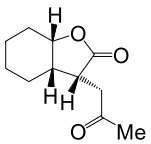
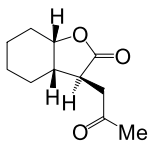
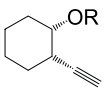
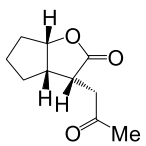
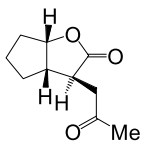
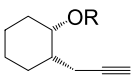
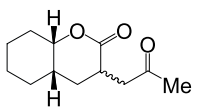
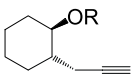
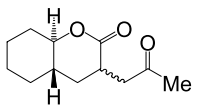
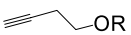
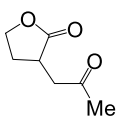
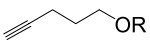
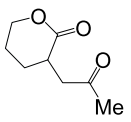
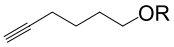
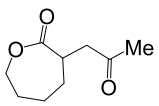
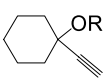
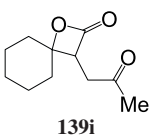
Later, Norton et al. developed a general method of α-methylenelactone **142** synthesis in mild conditions, which was based on cyclocarbonylation of ethynyl alcohols on organopalladium complexes as catalysts[76,77] (Scheme 59).

A comparative study of the ability of the various catalytic systems to cyclocarbonylate acyclic and cyclic alcohols showed that system comprising $PdCl_2$, anhydrous $SnCl_2$ and 2 equiv. of a tertiary phosphine in acetonitrile is the most favoured. In this system, not only α-methylene-γ-lactones, but also -δ-lactones, of various structure in *cis*- and *trans*-fused rings can be synthesised in rather high yields, if the substrate concentration is kept sufficiently low (0.1–1.0 M), to direct the reaction into an intramolecular cyclisation. A study of the cyclocarbonylation mechanism showed that a carboalkoxy intermediate species is initially formed from



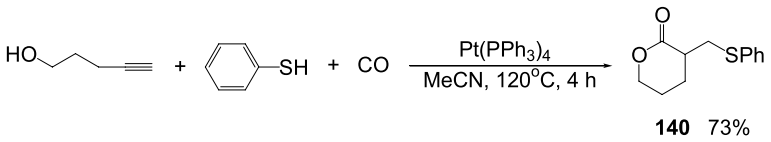
Scheme 56. (i) (1) **138** (1.2 equiv), MeCN, 70 °C, 0.5 h. (2) $[FeCl_2(DMF)_3][FeCl_4]$ (3 equiv.).

Table 4. Construction of lactones **139** from various alcohols and silyl ethers

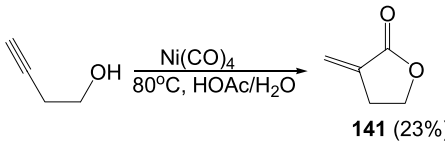
	Substrate **137**	Products **139**, **139′**	Yield (%)	Ratio (139:139′)
a		 **139a**  **139′**	R=H 85	92:8
b		 **139b**  **139b′**	R=H 94 R=TBS 76	94:6 48:52
c		 **139c**  **139c′**	R=H 94 R=TBS 96	93:7 98:2
d		 **139d**	R=H 78 R=TBS 100	70:30 85:15
e		 **139d**	R=H 89 R=TBS 57	59:41 66:34
f		 **139f**	R=H 86 R=TBS 43	
g		 **139g**	R=H 62 R=TBS 53	
h		 **139h**	R=H 63	
i		 **139i**	R=H 30	

Pd(II), CO and the acetylene alcohol, followed by intramolecular *cis* addition to the triple bond[77,78] (Scheme 60).

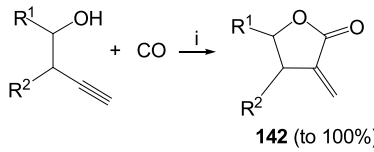
Competitive intermolecular insertion of the triple bond in another substrate can occur, leading to dimeric and polymeric products. Cleavage of the vinyl-palladium bond was achieved by the initially generated proton and the product was then obtained in addition to the regeneration of the initial Pd(II) complex. In the course of their mechanistic



Scheme 57.



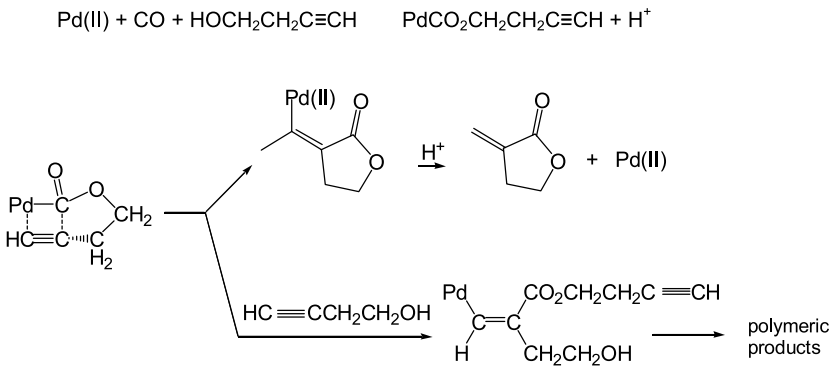
Scheme 58.



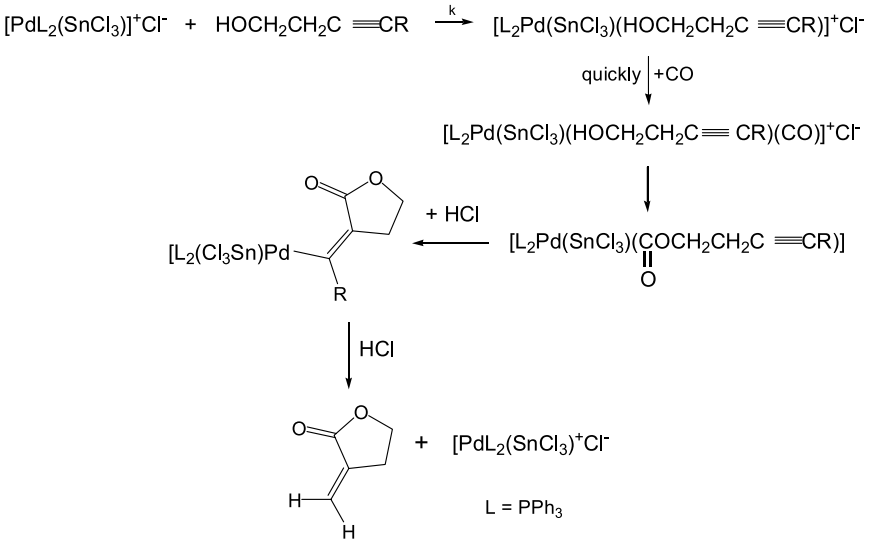
Scheme 59. R^1, R^2=H, $(CH_2)_2Br$, $(CH_2)_2CH=CH_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$. I: $PdCl_2$ (0.07 equiv.), $SnCl_2$ (0.07 equiv.), PPh_3 (or PBu_3) (0.14 equiv.), CO (to 7.8 atm), MeCN, 65–75 °C.

studies, the authors proposed a much more efficient Pd(II) catalyst system with $SnCl_2$ as a cocatalyst which has a role in labilising the palladium coordination sphere. As in PdI_2/Bu_3P/MeCN catalyst system, the rate-determining step is evidently the uptake of CO by Pd. Similarly, in the second catalyst system ($PdCl_2/2Ph_3P/SnCl_2$/MeCN), the rate-determining step is coordination of the substrate, followed by rapid uptake of CO and completion of the cyclocarbonylation reaction[78] (Scheme 61).

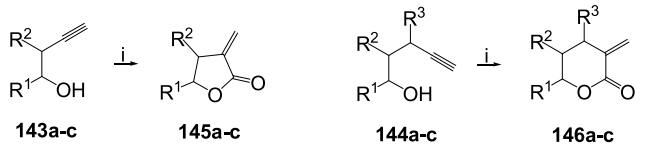
Dupont et al. have shown that the carbonylation of terminal 3-alkyn-1-ols **143a-c** and 4-alkyn-1-ols **144a-c** by $Pd(OAc)_2$ associated with 2-(diphenylphosphino)pyridine (2-$PyPPh_2$) dissolved in organic solvents, or in 1-butyl-3-methyl imidazolium ionic liquids, afforded quantitatively and selectively the *exo*-α-methylene-γ- and -δ-lactones **145a-c**, and **146a-c**, respectively (Scheme 62). When the reactions were performed in ionic liquids (biphasic conditions), the lactones **145a-c**, and **146a-c** were isolated



Scheme 60.



Scheme 61.



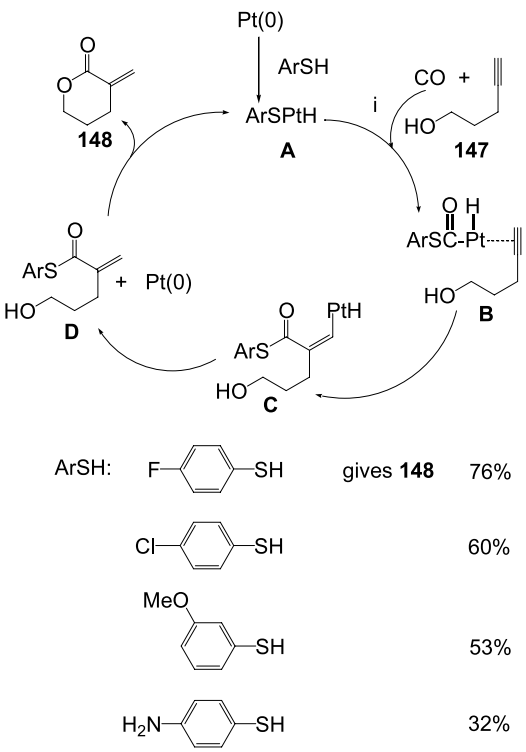
Scheme 62. 145 a R^1=R^2=H (97% yield); **b** r^1=Me, R^2=H (99%); **c** R^1 R^2=$(CH_2)_4$ (99%). **146 a** R^1=R^2=R^3=H (98%); **b** R^1 R^2=$(CH_2)_4$, R^3=H (50%); **c** R^1=H, R^2 R^3=$(CH_2)_4$ (93%). (i) $Pd(OAc)_2$/2-$PyPPh_3$/$MePhSO_3$-H/alkynol=1/10 /10 /1000, toluene, CO (25 atm), 60 °C, 2 h.

by simple distillation, which enabled the re-use of the ionic catalyst solution.[79]

The carbonylative lactonisation of 5-hydroxy-1-pentyne **147** to produce α-methylene-δ-lactone **148** has been found to proceed efficiently by using catalytic $Pt(PPh_3)_4$ in the presence of small amounts of aromatic thiols. A possible reaction pathway for this carbonylative lactonisation is depicted in Scheme 63 and comprises: (1) oxidative addition of ArSH to low-valent platinum generating the ArS–[Pt]–H species (**A**), which undergoes coordination of the hydroxyacetylene **147** and insertion of CO to form species **B**; (2) regioselective acylplatination leading to species **C**, followed by reductive elimination to produce the α,β-unsaturated thioester **D** and Pt(0); and (3) intramolecular cyclisation of **D** to provide α-methylene-δ-lactone **148** and ArSH, the latter adding oxidatively to Pt^0 and regenerating the catalyst **A**.[72]

26. Stereoselective synthesis of (*Z*)-α-(alkoxycarbonyl)methylene-β- and -γ-lactones

(*Z*)-α-(Alkoxycarbonyl)methylene-β- **150** and -γ-lactones **152** can be obtained in fair to excellent yields using the catalytic system (PdI_2/KI) to efficiently catalyse the oxidative dialkoxycarbonylation of propynyl alcohols (α,α-dialkyl-substituted or α-monoalkyl-substituted) with a sufficiently bulky alkyl group **149** and but-3-yn-1-ols **151**, respectively. The reactions are carried out in alcoholic media under mild conditions (70–80 °C and 20 atm of a 3:1 mixture of CO and air) (Scheme 64).[80,81] Possible reaction pathways are discussed.[80,81]



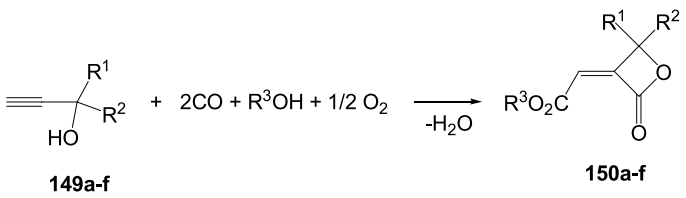
Scheme 63. (i) $Pt(PPh_3)_4$ (3 mol%), ArSH (10 mol%), MeCN, 120 °C, CO (30 atm), 4 h.

The presence of alkyl substituents α to the triple bond is essential in order to achieve a high selectivity for the β-lactones **150**. The yields of the β-lactones derived from α-monoalkyl-substituted propynyl alcohols are very low if the alkyl group is not sufficiently hindered. But-3-yn-2-ol **149f** produced only 2% of the corresponding β-lactone **150f** at 80% conversion. The maleic diester **153** (50%), its cyclic tautomer **154** (9%), the fumaric derivative **155** (12%) and the γ-lactone **156** (6%) accounted for the converted substrate (Scheme 65). In contrast to the propynyl alcohols, α substitution of the triple bond in but-3-yn-1-ols **151** is not necessary in order to direct the carbonylation process towards ring closure to give the γ-lactones selectively, and but-3-yn-1-ol **151a**, pent-4-yn-2-ol **151b** and *cis*-2-ethynylcyclopentan-1-ol **151d** were, in fact, converted into their corresponding γ-lactones **152a**, **152b** and **152d** in excellent yields. When the dialkyl substitution α to the triple bond was as in **151c**, the reaction was slower and the product yield of the γ-lactone **152** was lower. If the cyclisation is not favoured by molecular geometry, as in the case of *trans*-2-ethynylcyclopentan-1-ol **151e**, the product distribution changes, favouring the maleate, and the γ-lactone **152e** is the byproduct.[80]

Palladium (II)-catalysed dicarbonylation of the 4-(trimethylsilyl)-3-butyn-1-ols **157a** and **157b** in the presence of propylene oxide and ethyl orthoacetate in methanol–dichloromethane under a carbon monoxide atmospheric pressure afforded the *cis*-dicarbonylated α-methylene-γ-butyrolactones **158a**, and **158b**, respectively. On the other hand, the 4-alkyl- and 4-aryl-3-butyn-1-ols **157c-g**, undergo *trans*-alkoxycarbonylation across the triple bond and selectively furnish the (*E*)-tetrasubstituted α-methylene-γ-butyrolactones **159c-g** (Scheme 66).[82]

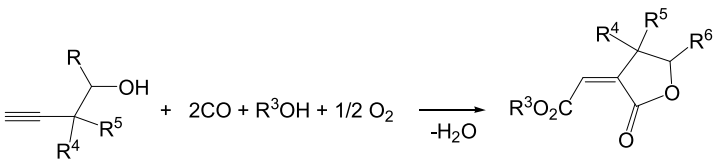
27. Formation of α-(triorganosilyl)methylene-β-, -γ- and -δ-lactones

Cyclocarbonylation of the acetylenic alcohols **160**, **163** and **164** with the assistance of an appropriate base and $Rh_4(CO)_{12}$ gave the α-(triorganosilyl)-methylene-β- **161**, -γ- **165**, and -δ- **166** lactones together with the byproducts **167** and **168**. Lactone formation depends on both steric and electronic factors and the ratio of the β-lactone **161** to the 3-silylpropenal **162** was markedly affected by the silane and the base employed in the carbonylation of the acetylenic alcohols **160**. An improvement in the β-lactone selectivity was attained using either a more bulky silane, such as *t*-$BuMe_2SiH$, or a stronger base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[83] (Scheme 67). Carbonylation of **160** without a base, however, resulted in the formation of **162** selectively.



149a-f **150a-f**

a $R^1 = R^2 = Me$	**a** $R^1 = R^2 = R^3 = Me$ (80%)
b $R^1 = Et$, $R^2 = Me$	**b** $R^1 = Et$, $R^2 = R^3 = Me$ (76%)
c R^1 ñ $R^2 = (CH_2)_5$	**c** R^1 ñ $R^2 = (CH_2)_5$, $R^3 = Me$ (57%)
d $R^1 = H$, $R^2 = CHEt_2$	**d** $R^1 = H$, $R^2 = CHEt_2$, $R^3 = Me$ (52%)
f $R^1 = H$, $R^2 = Me$	**e** $R^1 = R^2 = Me$, $R^2 = R^3 = Me$ (22%)
	f $R^1 = H$, $R^2 = R^3 = Me$ (2%)



151a-e **152a-e**

a $R^4 = R^5 = R^6 = H$	**a** $R^4 = R^5 = R^6 = H$, $R^3 = Me$ (86%)
b $R^4 = R^5 = H$, $R^6 = Me$	**b** $R^4 = R^5 = H$, $R^3 = R^6 = Me$ (94%)
c $R^4 = R^5 = Me$, $R^6 = H$	**c** $R^3 = R^4 = R^5 = Me$, $R^6 = H$ (73%)
d $R^4 = H$, $R^5 R^6 = (CH_2)_3$(*cis*)	**d** $R^4 = H$, $R^5 R^6 = (CH_2)_3$ (*cis*), $R^3 = Me$ (93%)
e $R^4 = H$, $R^5 R^6 = (CH_2)_3$(*trans*)	**e** $R^4 = H$, $R^5 R^6 = (CH_2)_3$ (*trans*), $R^3 = Me$ (28%)

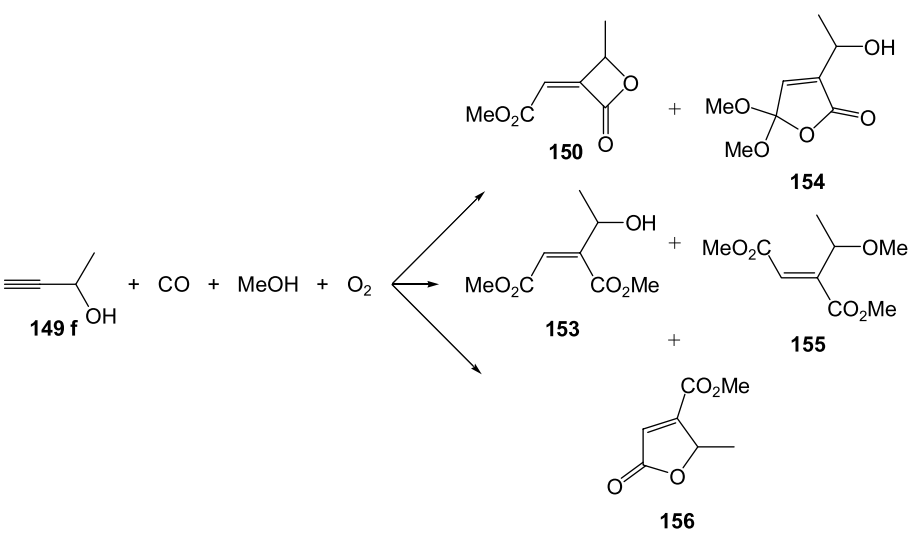
Scheme 64.

The γ-lactone **165** is derived from the homopropargyl-type alcohols **163** with the employment of Me_2PhSiH and Et_3N. Although the combined use of *t*-$BuMe_2SiH$ and Et_3N is required for the formation of the six-membered ring α-silylmethylene, this method is applicable for the selective synthesis of the δ-lactone **166**. The intermediate **A** is proposed to be the common intermediate to give the lactone and propenal derivatives.

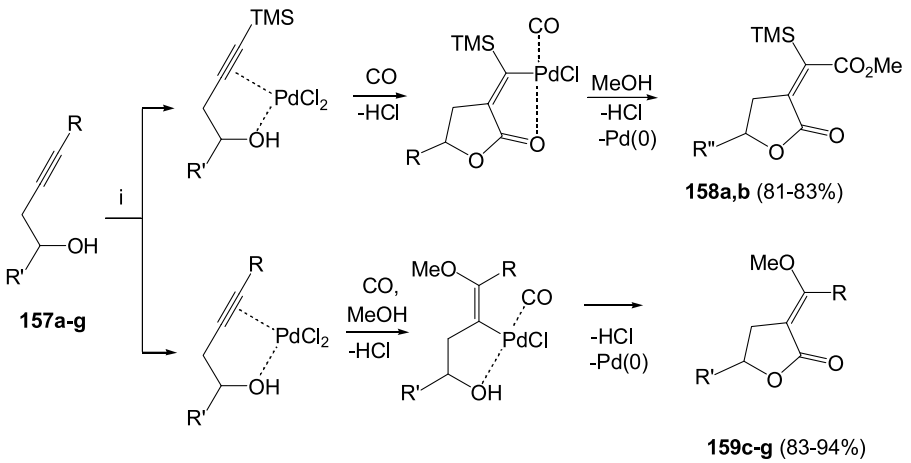
28. Selective synthesis of furan-2(5*H*)-ones

Carbonylation of 2-methylbut-3-yn-2-ol catalysed by $Co_2(CO)_8$ in benzene proceeds with low yield, but 100% selectively, giving 5,5-dimethylfuran-2(5*H*)-one **169** (Scheme 68).[84]

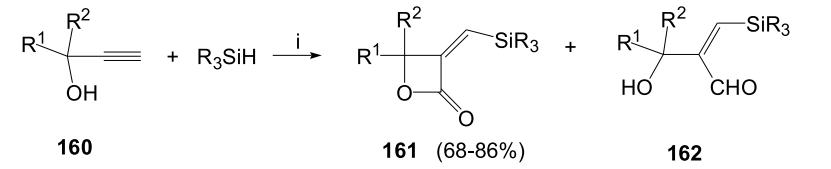
The unsaturated lactone **171** is formed when the alkynol **170**

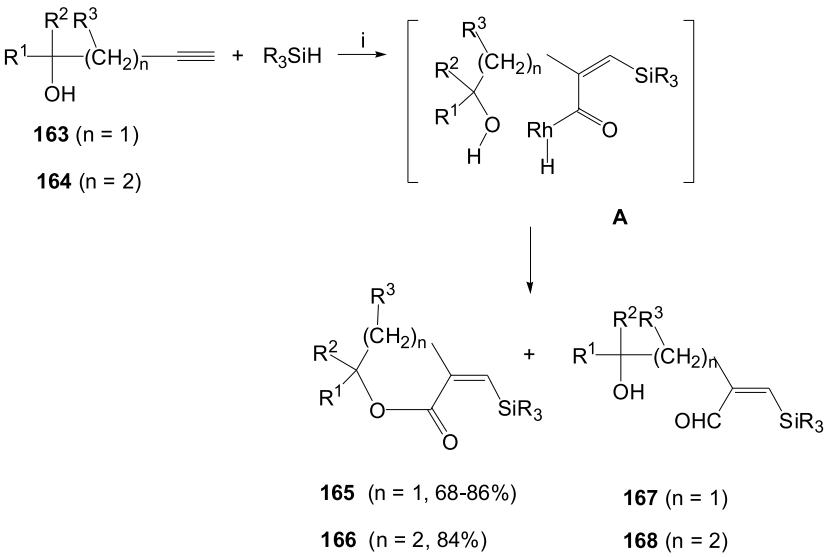


Scheme 65.

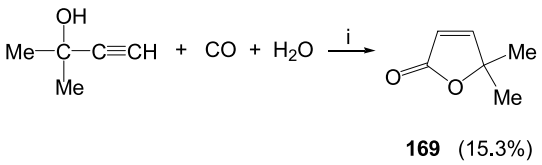


Scheme 66. **a** R=TMS (trimethylsilyl), R=H; **b** R=TMS, R=Me; **c** R=Me, R′=H; **d** R=Et, R=H; **e** R=Et, R=Me; **f** R=t-Bu, R=Me; **g** R=Ph, R=Me. (i) CO (1 atm), $PdCl_2$ (0.01–0.1 equiv.), $CuCl_2$ (3 equiv.), propylene oxide (5 equiv.), $MeC(OEt)_3$ (0.4 equiv.), MeOH, rt.

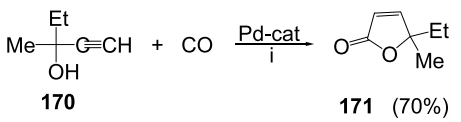




Scheme 67. R^1, R^2=H, Me, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$; R=Me, Ph, tBu, Et, iPr. (i) CO (15–40 kg/cm^2), base (1 equiv. Et_3N, 0.1 equiv. DBU or DABCO—1,4-diazabicyclo[2.2.2]octane), $Rh_4(CO)_{12}$ (0.001 equiv.), 100 °C, benzene.



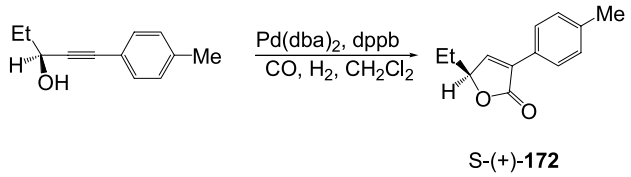
Scheme 68. (i) 150°, 100 atm, $Co_2(CO)_8$ (5 mol%) benzene.



Scheme 69. (i) $Pd(dba)_2$, dppb, DME, CO (20 atm), 150 °C, 48 h.

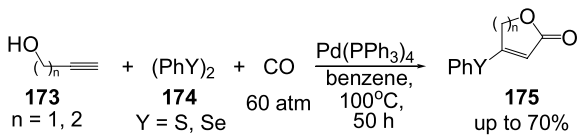
is carbonylated with the palladium(0) catalyst, bis(dibenzylidenacetone)palladium (dba), and 1,4-bis(diphenyl-phosphino)butane (dppb) in 1,2-dimethoxyethane (DME) (Scheme 69).[85]

This method was used for the synthesis of unnatural (*S*)-incrustoporin **172**, the enantiomer of the antifungal antobiotic isolated from the basidiomycete *Incrustoporia carneola* (Scheme 70).[86,87] Ethynyl alcohols also produce 2(5*H*)furanones upon carbonylation using $Pd(MeCN)_2$-$(PPh_3)_2(BF_4)_2$ as catalyst.[88]



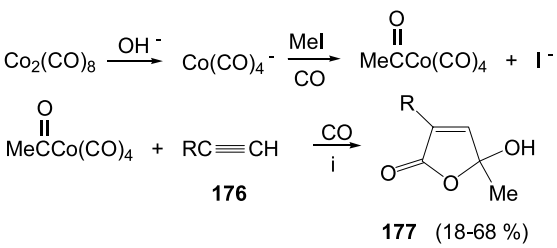
Scheme 70.

A one-pot lactonisation of the alkynols **173** in the presence of the thio–thio or seleno–seleno organic compounds **174** and carbon monoxide occurred to furnish the substituted unsaturated lactones **175** in up to 70% yield (Scheme 71).[89]



Scheme 71.

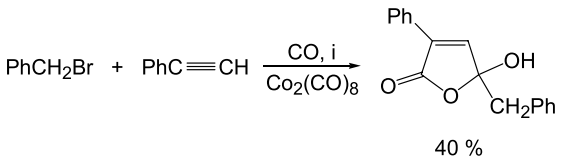
The alkynes **176** react smoothly with CO and MeI in a liquid–liquid two-phase system to yield regioselectivly the corresponding but-2-enolides **177** (Scheme 72), most probably via the intermediate formation of an acylcobalt complex.[90,91]



Scheme 72. R=Ph, Cy, 17-testosteronyl. (i) 5 N NaOH/benzene, CTAB (cetyltrimethylammonium bromide), rt, CO (1 atm).

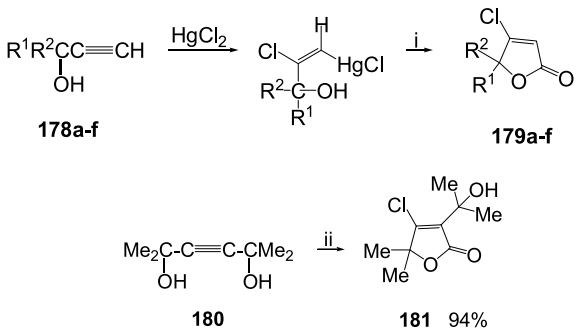
When benzyl bromide was used, no but-2-enolide was formed, due to the fast hydrolysis of the acylcobalt intermediate prior to the alkyne complexation, and phenylacetic acid was the only product obtained. This inconvenience was circumvented by performing the reaction in the absence of water in a solid–liquid system using a new kind of chelating agent, $N[(CH_2)_2O(CH_2)_2OMe]_3$ (TDA), which has the same properties as a crown ether but without the toxicity and the work-up difficulties encountered with the macrocyclic catalysts[92] (Scheme 73).

The mercuration and subsequent carbonylation of the



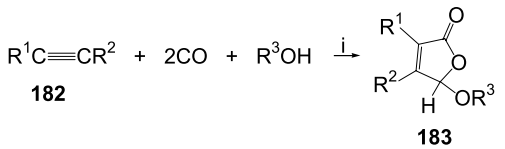
Scheme 73. (i) $Co_2(CO)_8$ (30 mol%), NaOH, TDA (6 mol%), toluene, 60 °C, 12 h, CO (1 atm).

propargylic alcohols **178** or the diol **180** has provided another route to the butenolide (4-chloro-furan-2(5*H*)-one) ring system **179** and **181** in quantitative yields (Scheme 74). Carbonylation can be effected using stoichiometric amounts of palladium chloride and 1 atm of carbon monoxide, or only catalytic amounts of palladium chloride if cupric chloride is used as a re-oxidant and benzene as the solvent.[93,94]



Scheme 74. (i) $PdCl_2$ (1 equiv.), LiCl (2 equiv.), THF, 5 °C, 24 h, MgO (1 equiv.) or none. **179a** R^1=R^2=H, (96%); **b** R^1=R^2=Me (99%); **c** R^1=Me, R^2=Et, (98%); **d** R^1 R^2=$(CH_2)_4$, (96%); **e** R^1 R^2=$(CH_2)_5$ (95%); **f** R^1 R^2=$(CH_2)_6$ (81%). (ii) $HgCl_2$, CO, $LiCl_3$ (2 equiv.), $PdCl_3$, THF, reflux, 5 h, MgO.

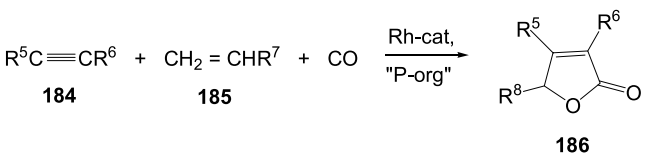
The rhodium carbonyl-catalysed carbonylation of acetylenes in alcohols **182**, giving the 5-alkoxyfuran-2-(5*H*)-ones **183** in satisfactory yields, has been reported (Scheme 75).[95–97] Combinations of rhodium catalysts with various bases were examined and the $Rh_4(CO)_{12}$/NaOAc system was found to be the most suitable catalytic system.[97]



Scheme 75. (i) CO (50 atm), 125 °C, 6 h, $Rh_4(CO)_{12}$ (0.1–0.2 mol%)/-NaOAc (5–10 mol%). **183** R^1=R^2=Ph, R^3=Me (86%); R^3=Et (87%); R^3=*n*-Pr (65%); R^3=*i*Pr (60%); R^3=C_8H_{17} (31%); R^1=R^2=Me, R^3=Et (67%); R^1=R^2=Et, R^3=Et (60%); R^1=Ph, R^2=Me, R^3=Me (54%); R^3=Et (78%); R^1=Me, R^2=Ph, R^3=Me (21%); R^3=Et (15%).

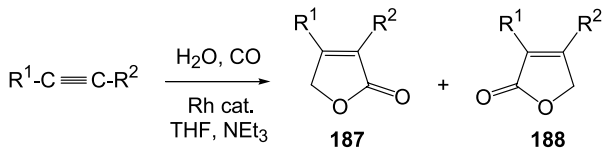
The reaction of the acetylene analogue **184** and the alkenes **185** with CO in the presence of rhodium catalysts and organophosphoric compounds [$PR^1R^2R^3$, $P(OR^1)(OR^2)OR^3$ or $R^1R^2P(CH_2)PR^3R^4$, R^1–R^4=H, alkyl, n=1–4] gives the unsaturated lactones **186** in high yields (Scheme 76).[98]

Doyama, et al. have proposed a general method for the selective synthesis of furan-2(5*H*)-ones **187** and **188** from acetylenes that have been elaborated by water vapour and carbon monoxide (100 atm) in THF containing triethylamine at 100 °C in the presence of a rhodium carbonyl



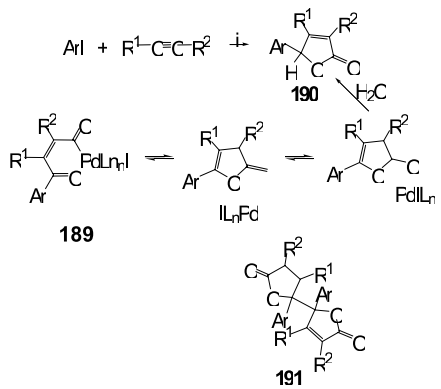
Scheme 76. R^5, R^6=H, Alkyl, Aryl, Silyl, Alkoxycarbonyl, Acyl; R^7=H, Hal, Alkyl, Alkoxycarbonyl, CN, Acyl; R^6=$CH_2CH_2R^7$ or $CHMeR^7$.

cluster catalyst[99,100] (Scheme 77). The isomer ratio of the formed furanones **187** and **188** is dependent on the electronic and steric nature of the substituents, such as the rhodium carbonyl clusters [$Rh_4(CO)_{12}$ and $Rh_6(CO)_{16}$], which were the most efficient among the other tested transition metal complexes tested. Ruthenium carbonyls showed a very low activity and cobalt and iron carbonyls were almost inactive for the present reaction. The presence of amines such as diethylamine or triethylamine is essential for the selective synthesis of furanones. The absence of amines resulted in a marked decrease in both the catalytic activity and product selectivity.

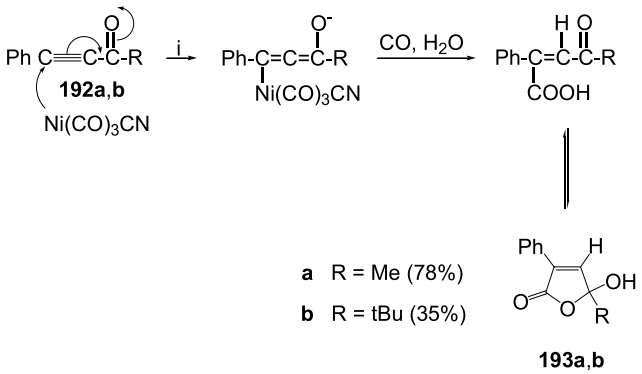


Scheme 77.

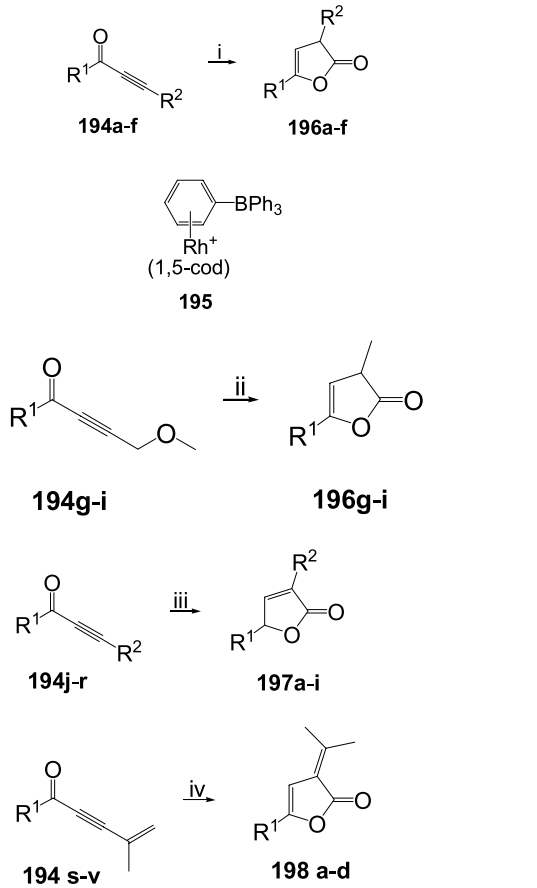
Negishi et al. have reported[101] that the reaction of an internal alkyne—organic halide mixture with CO in the presence of a Pd–phosphine catalyst, for example, Cl_2-$Pd(PPh_3)_2$, can give rise to an acylpalladium derivative that can be represented by **189** as an intermediate which is converted into the corresponding 2-butenolides **190** in the presence of water (H donor). Either in the absence of water (or any other suitable H source) or in the presence of some factors disfavouring the butenolide formation, the same reaction afforded the corresponding dimeric product **191** (Scheme 78).



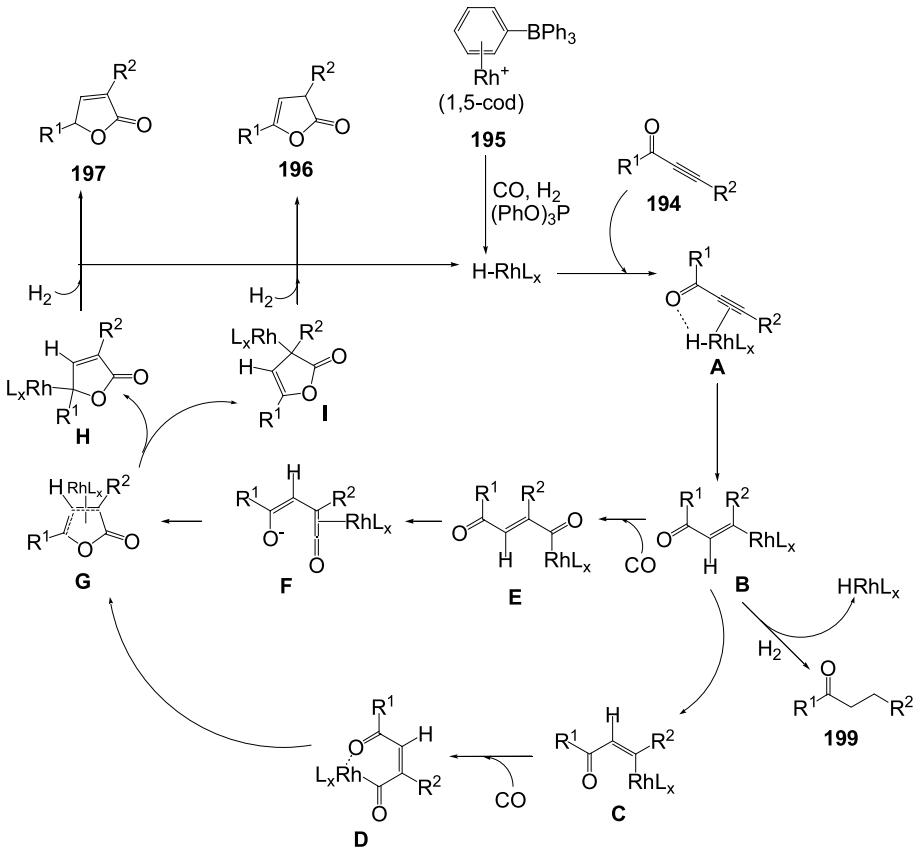
Scheme 78. (i) CO (20 atm), $Cl_2Pd(PPh_3)_2$ (5 mol%), H_2O (1 equiv.), NEt_3 (8 equiv.) or $NaHCO_3$ (4 equiv.), benzene, 130 °C, 20 h. **190**, **191a-c** R^1=R^2=*n*-Pr; **a** Ar=*p*-An (combined yield 66%); **b** Ar=*m*-Tol (comb. yield 50%); **c** Ar=*p*-ClC_6H_4 (comb. yield 40%); **d** R^1=R^2=Bn, Ar=*m*-Tol (comb. yield 42%); **e** R^1=Bu, R^2=*p*-An, Ar=Ph, (comb. yield 65%, **190**:**191**=89:11); **f** R^1=Bu, R^2=R^3=*p*-An, (comb. yield 65%, **190**:**191**=91:9); **g** R^1=Bu, R^2=*p*-An, R^3=*p*-$MeO_2C_6H_4$, (comb. yield 35%, **187**:**188**=91:9); **h** R^1=$SiMe_3$, R^2=Pr, R^3=Ph, (comb. yield 39%, **190**:**191**=94:6); **i** R^1=$SiMe_3$, R^2=Pr, R^3=*p*-An, (comb. yield 37%, **190**:**191**=94:6).



Scheme 79. (i) $Ni(CN)_2{\cdot}4H_2O$ (10 mol%), CO (1 atm), PhMe/5 N NaOH (1:1), TBAB (3 mol%).



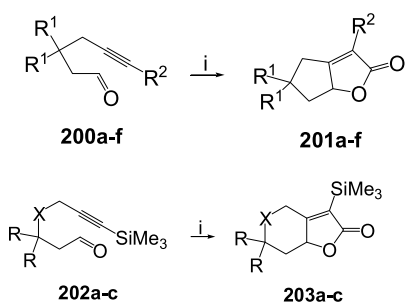
Scheme 80. 194, **196 a** R^1=Me, R^2=Et, (91%); **b** R^1=iPr, R^2=Bu (88%); **c** R^1=CH-Et-Bu, R^2=Bu, (83%); **d** R^1=Cy, R^2=n-Bu (63%); **e** R^1=tBu, R^2=Bu, (64%); **f** R^1=Ph, R^2=Bu (63%). (i) **194** (1.5 mmol), **195** (0.03 mmol) (2 mol%), $(PhO)_3P$, 0.18 mmol (32 mol%), CH_2Cl_2 910 ml), CO (38.5 atm), H_2 (3.5 atm), 90 °C, 21 h. **194**, **196 g** R^1=iPr (92%); **h** R^1=CH-Et-Bu, (91%); **i** R^1=tBu (89%). (ii) **194** 1.5 mmol, **195**, 2 mol%; $(PhO)_3P$, 8 mol%; Cu_2Cl_2 10 ml; CO (17.5 atm), H_2 (3.5 atm), 70 °C, 24–36 h. **197 a** R^1=Me, R^2=Ph (83%); **b** R^1=iPr, R^2=Ph (88%); **c** R^1=CH-Et-Bu, R^2=Ph (87%); **d** R^1=Cy, R^2=Ph (84%); **e** R^1=tBu, R^2=Ph (85%); **f** R^1=R^2=Ph (61%); **g** R^1=2-Fur, R^2=Ph, (67%); **h** R^1=Ph, R^2=Bu (61%); **i** R^1=2-Fur, R^2=Bu (68%). (iii) **194** 1.5 mmol, **195**, 2 mol%; $(PhO)_3P$, 32 mol%; Cu_2Cl_2, 10 ml; CO (38.5 atm), H_2 (3.5 atm), 120 °C, 24–48 h. **198 a** R^1=iPr (71%); **b** R^1=CH-Et-Bu, (76%); **c** R^1=tBu (69%); **d** R^1=Ph (75%). (iv) **194** 1.5 mmol, **195**, 2 mol%; $(PhO)_3P$, 8 mol%; CH_2Cl_2 10 ml; CO (17.5 atm), H_2 (3.5 atm), 70 °C, 24 h.



Scheme 81.

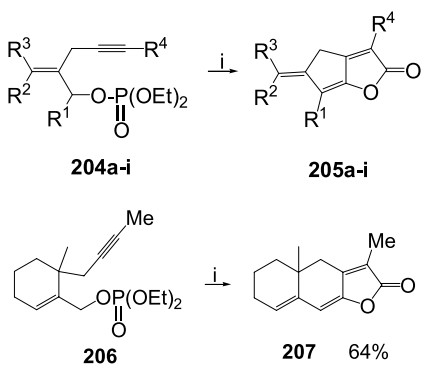
The α-keto alkynes **192a**,**b** without an α-H atom on the α-carbon atom to the alkynyl group are carbonylated in the presence of $Ni(CN)_2$ under phase-transfer conditions [toluene, 5 N NaOH, tetrabutyl-ammonium bromide (TBAB)] to give the unsaturated hydroxybutyrolactones **193a**,**b** (Scheme 79).[102]

The cyclohydrocarbonylaton of the α-keto alkynes **194a**-**r** was readily accomplished by the zwitterionic rhodium complex **195** and triphenyl phosphite in the presence of CO and H_2. The temperature and pressure required were sometimes milder than those previously reported for other reactions. Good chemo- and regioselectivity were observed for a variety of multifunctionalised alkynes to produce the 2(3*H*)-furanones **196a**-**i**, 2(5*H*)furanones **197a**-**i** and 2-furanones **195a**-**d** as the sole products (Scheme 80).[103]



Scheme 82. 200, **201 a** R^1=COOEt, R^2=$SiMe_3$ (82%); **b** R^1=COOEt, R^2=Ph (62%); **c** R^1=COOEt, R^2=$(CH_2)_2OCH_2Ph$ (80%); **d** R^1=COOEt, R^2=$(CH_2)_2C{\equiv}CSiMe_3$ (91%); **e** R^1=COOEt, R^2=CH=CHPh (83%); **f** R^1=H, R^2=$SiMe_3$ (92%). **202**, **203 a** R=COOEt, X=CH_2, (93%); **b** R=Me, X=O (89%); **c** R=H, X=NTs (74%). (i) CO (10 atm), $Ru_3(CO)_{12}$ (2 mol%), toluene, 160 °C, 20 h.

The authors[103] have indicated that a number of factors influenced the preparation of the unsaturated γ-lactones **196**-**198** from the α-keto alkynes **194**. Only a five-membered ring was formed, indicating that the acyl-rhodium intermediate always originates at the triple bond carbon close to R^2. The nature of R^1 and R^2 substantially influences both the formation of the unsaturated lactone and hydrogenation. The authors proposed a mechanism (Scheme 81) for the preparation of furanones from α-keto alkynes **194** which involves the following steps: (1) the rhodium hydride complex $HRhL_x$ binds to the triple bond of the alkynone with a possible weak H-bonding interaction to the ketone functionality **A**; (2) intramolecular addition of the rhodium hydride to the triple bond of the α-keto alkyne afford the E-isomer **B**; (3) depending upon the extent of the interaction between R^1 and R^2, one of two possible pathway may occur in the next stage of the process; appreciable steric interaction between R^1 and R^2 would destabilise **B** resulting in further hydrogenation of the alkenyl intermediate to the ketone **199** and regeneration of $HRhL_x$. Whilst if **B** is stable, carbonylation **E** and rearrangement to the zwitterionic ketene **F**, or isomerisation **C** and carbonylation **D**, would generate **G** via intramolecular cyclisation and (4) either the rhodium–furanone complex **H** or **I** will form. The reaction of either rhodium complex with H_2 affords the 2(3*H*)-furanone **196** or the 2(5*H*)-furanone **197** and regeneration of the rhodium hydride.



Scheme 83. 204, **205 a** R^1=R^2=R^3=H, R^4=Bu (73%); **b** R^1=R^2=R^3=H, R^4=Cy (94%); **c** R^1=R^2=R^3=H, R^4=tBu (87%); **d** R^1=R^2=R^3=H, R^4=Me (52%); **e** R^1=R^2=H, R^3=Bu, R^4=Me (80%, *Z*/*E*=2:1); **f** R^1=Bu, R^2=R^3=H, R^4=Me (88%, *Z*/*E*=2:1); **g** R^1=H, R^2=H, R^3=Ph, R^4=Me (50%, *Z*/*E*=1:1); **h** R^1=H, R^2=R^3=R^4=Me (73%); **i** R^1+R^2=CH_2CMe_2-CH_2, R^3=H, R^4=Me (72%). (i) CO (1 atm), [{(η^3-C_3H_5)PdCl}$_2$], CyNMe (2 equiv.), THF, 80 °C, 12 h.

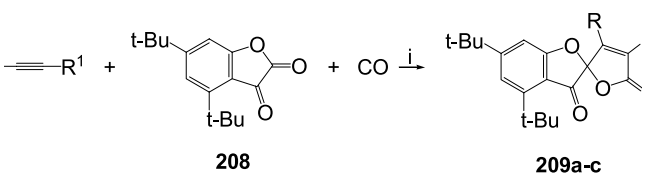
29. Synthesis of bi- and polycyclic α,β-unsaturated γ- and δ-lactones

Chatani et al. have demonstrated the first example of a Ru-catalysed cyclocarbonylation of yne-aldehydes **200a**-**f**, **202a**-**c** with CO to bicyclic γ-butenolides **201a**-**f**, and **203a**-**c** in high yields (Scheme 82).[104]

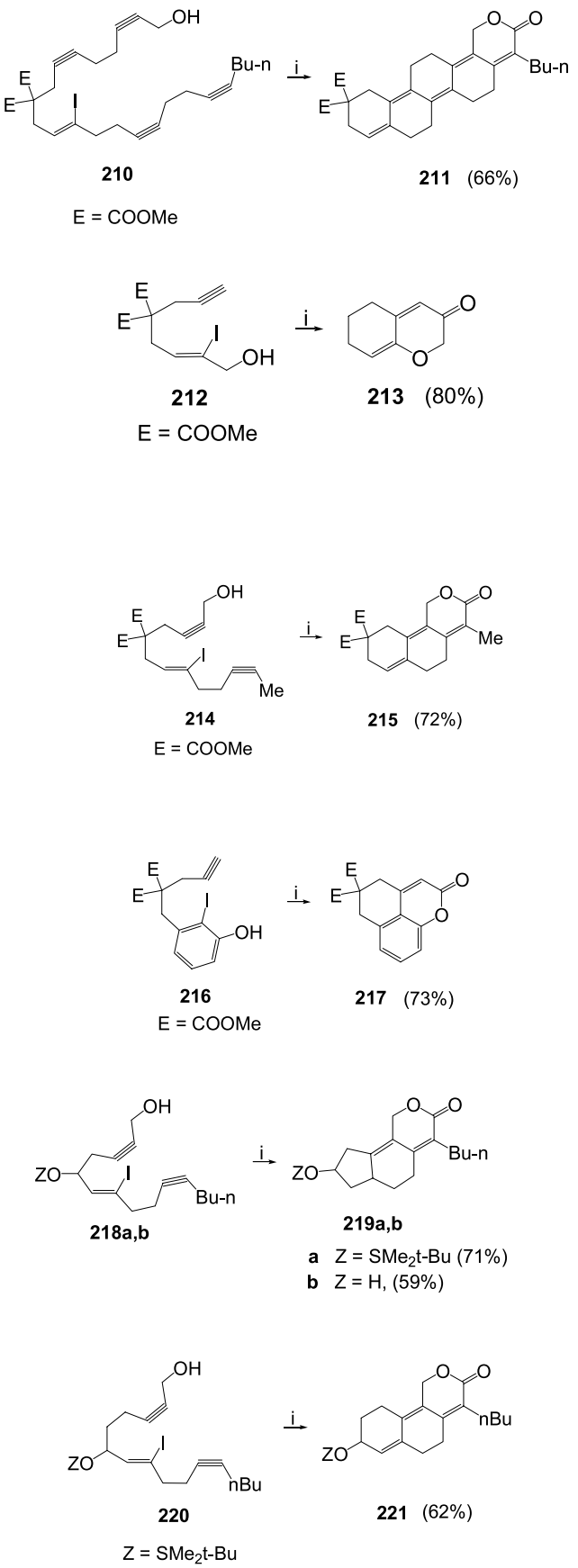
Recently, Kamitani and coworkers have developed a new method for the construction of the highly unsaturated bicyclic lactones **205a**-**i**, and **207** by the Pd-catalyzed carbonylation of 2-propargylallyl phosphates **204a**-**i**, **206** (Scheme 83). The reaction proceeds smoothly, even under mild conditions.[105]

The ruthenium-catalysed reaction of the benzofuran-2,3-dione derivative **208** with CO and alkynes results in a carbonylative [2+2+1] cycloaddition in which the ester-carbonyl group is incorporated into a two-atom assembling unit to give the spirolactone derivatives **209a**-**c** (Scheme 84).[106]

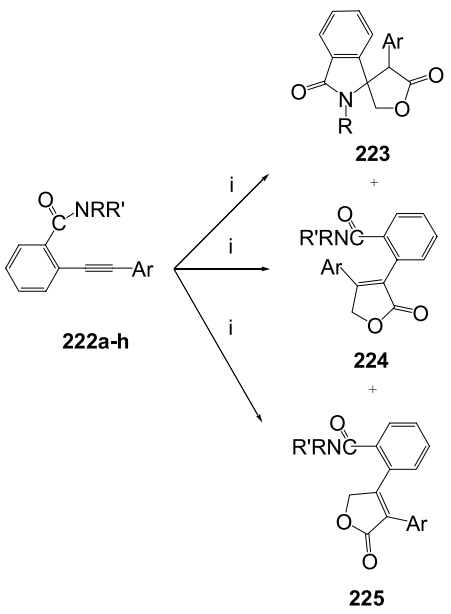
Sugihara et al. have reported[107] that the catalytic cyclic carbopalladation of alkynes can proceed under the conditions for carbonylation of the organopalladium without premature incorporation of CO and the in situ regeneration of a Pd–phosphine catalyst can be accomplished by termination of the carbopalladation cascade via deferred carbonylative esterification, such as the conversion of **210** to **211** (Scheme 85) and the related conversion of **212**, **214**, **216**, **218a**,**b** and **220** to **213**, **215**, **217**, **219a**,**b** and **221**, respectively.



Scheme 84. 209 a R=R^1=Ph (83%); **b** R=Me, R^1=$SiMe_3$ (95%); **c** R=Ph, R^1=$SiMe_3$ (95%). (i) CO (5 atm, rt), $Ru_3(CO)_{12}$ (2.5 mol%); P(4-$CF_3C_6H_4$)$_3$ (7.5 mol%), toluene, 160 °C, 20 h.



Scheme 85. (i) CO (1.1 atm), $Cl_2Pd(PPh_3)_2$ (5 mol%), NEt_3 (2 equiv.), MeOH, 75 °C, 1 h.



Alkyne	R	Rí	Ar	Yield (%)		
222				**223**	**224**	**225**
a	H	H	Ph	34	45	-
b	Me	H	Ph	37	58	-
c	Ph	H	Ph	25	65	-
d	Me	Me	Ph	-	47	47
e	H	H	p-OMePh	33	55	-
f	H	H	p-CNPh	27	40	-
h	H	H	α-Naphth	21	40	16

Scheme 86. (i) $Rh_6(CO)_{16}$ (0.32 mol%), NEt_3 (1.4 equiv.), H_2O (5.5 equiv.), 1,4-dioxane, CO (100 atm), 80 °C, 3 days.

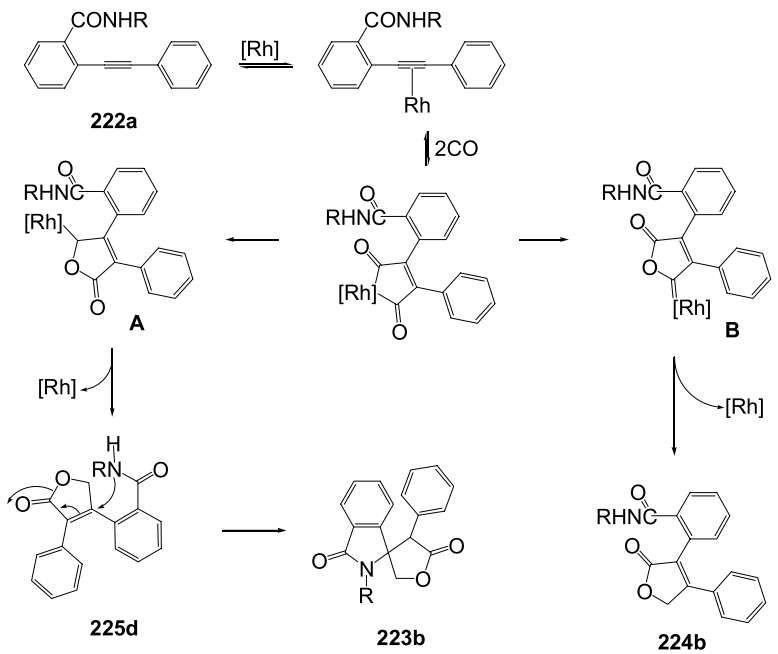
The authors have also shown[107] that the relative rates of various competing processes in a decreasing rate order are: CO insertion (and five- or six-membered lactonisation) ~5-*exo*- or 6-*exo*-alkyne carbopalladation>5-*exo*-alkyne acylpalladation>acylpalladium trapping with MeOH> intermolecular carbopalladation or acylpalladation.

Under water–gas shift reaction conditions, rhodium carbonyl-catalysed carbonylation of the 2-arylethynylbenzamides **222a-h** gave two kinds of products, the novel spiro compounds **223** and two 2(5*H*)-furanones **224** and **225** (Scheme 86), which were produced by cyclic carbonylation of a carbon–carbon triple bond. The spiro derivatives were formed by participation of the amide group adjacent to the carbon–carbon triple bond in the cyclisation process (Scheme 87).[108]

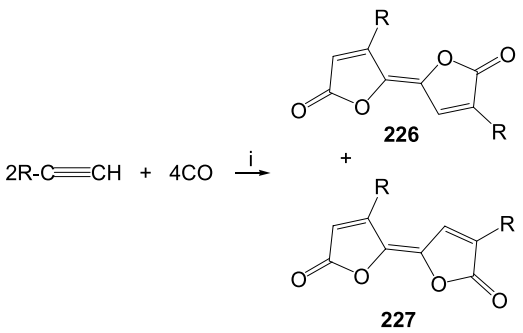
30. (*E*)- and (*Z*)-2,2′-Bifurylidene-5,5′-diones

Two groups have independently published the results of a catalytic reaction between CO and certain simple alkynes,[108–112] acetylene,[109,110,112] propyne,[109,111] hex-1-yne and some arylacetylenes[109]) that produces (*E*)- and (*Z*)-2,2′-bifurylidene-5,5′-diones **226** and **227** or bifurandiones,[109] octatrienediolides,[110–112] 5-(oxofuran-2(5*H*)-ylidene)furan-2(5*H*)-ones according to a previous and systematic nomenclature (Scheme 88).

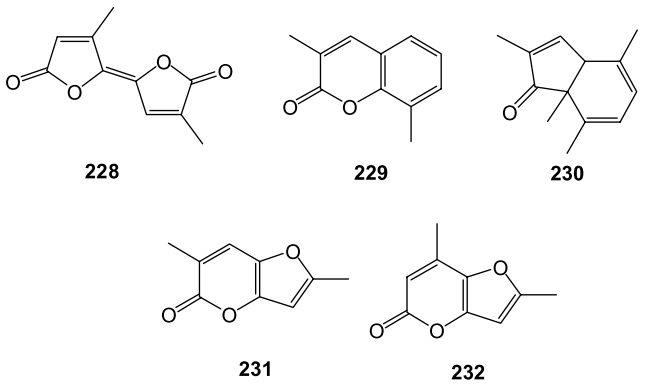
The reaction was performed at an approximate temperature of 100 °C and CO pressures of 100–300 and up to 1000 bar using $[Co_2(CO)_8]$ as a catalyst. Polar aprotic solvents, such as MeCN, $MeNO_2$, acetone, *N*,*N*,*N*′,*N*′-tetramethylurea, esters and ethers, appear to be most suitable. When acetone was used as a solvent, the yields have been improved by adding phosphines or phosphates.[113] It was also shown that Co complexes are intermediates in the catalytic reactions that lead to the bifurylidenediones.[114,115] In the course of the



Scheme 87.



Scheme 88. R=H, Me, Bu, Ph, *p*-ClPh, *o*-MeOPh. (i) $Co_2(CO)_8$, 90–120 °C, 100–300 bar.



Scheme 89.

re-investigation of this [$Co_2(CO)_8$]-catalysed reaction between propyne and CO in acetone at 110° and 170 bar, five major products were produced: (*E*)-3,4′-dimethyl-2,2-bifurylidene-5,5-dione **228**, 3,5,8-trimethylcoumarin **229**, 3a,7a-dihydro-2,4,7,7a-tetramethyl-1*H*-inden-1-one **230**, 2,6-dimethyl-5*H*-furo[3,2-*b*]pyran-5-one **231** and 2,7-dimethyl-5*H*-furo[3,2-*b*]pyran-5-one **232**[116] (Scheme 89). In addition, the products distribution is strongly affected by the CO pressure and propyne concentration. The structures of **230**, **231** and **232** were established by X-ray diffraction.[116]

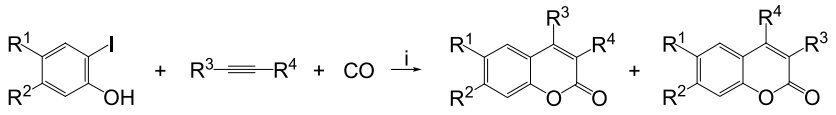
31. Synthesis of coumarins

Kadnikov and Larock have reported[117] that the palladium-catalysed coupling of *o*-iodophenols, internal alkynes, and carbon monoxide allowed the efficient synthesis of 3,4-disubstituted coumarins **233** and **234** bearing a variety of functional groups (Scheme 90).

Heterocyclic analogues of *o*-iodophenol are also effective in the carbonylative annulations of internal alkynes, 3-iodo-2-pyridone **235** affording the azacoumarin **236** in good yield (Scheme 91) in the same conditions.[117]

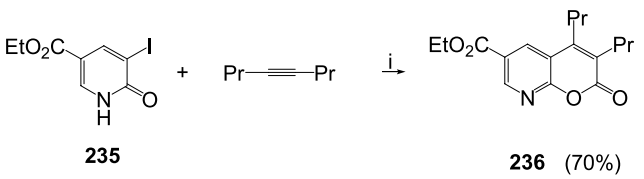
32. Synthesis of pyranopyrandiones

Kondo, et al. have shown[118] that unsymmetrical substituted pyranopyrandiones **237** were generally obtained in good to



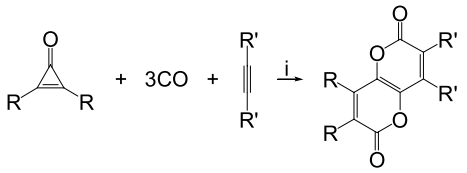
R^1	R^2	R^3	R^4	Time, (h)	**233**	**234**	combined % isolated yield (ratio **233**:**234**)
H	H	Pr	Pr	24	**a**	-	63
H	H	Ph	Ph	48	**b**	-	59
H	H	Me	Ph	24	**c**	**c**	72 (79:21)
H	H	Et	Ph	24	**d**	**d**	78 (72:28)
H	H	Me	tBu	24	**e**	-	9
H	H	CH_2OBn	Ph	24	**f**	**f**	65 (75:25)
H	H	Me	$SiMe_3$	24	**g**	-	43
H	H	Et	CH_3CO	24	**h**	**h**	61 (90:10)
CO_2Et	H	Pr	Pr	24	**i**	-	59
OMe	H	Pr	Pr	12	**j**	-	66
H	CO_2Me	Pr	Pr	6	**k**	-	62

Scheme 90. (i) Iodophenol (0.5 mmol), alkyne (2.5 mmol), pyridine (1.0 mmol), Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5 mol%) in DMF (5 ml), 120 °C.



235 **236** (70%)

Scheme 91.

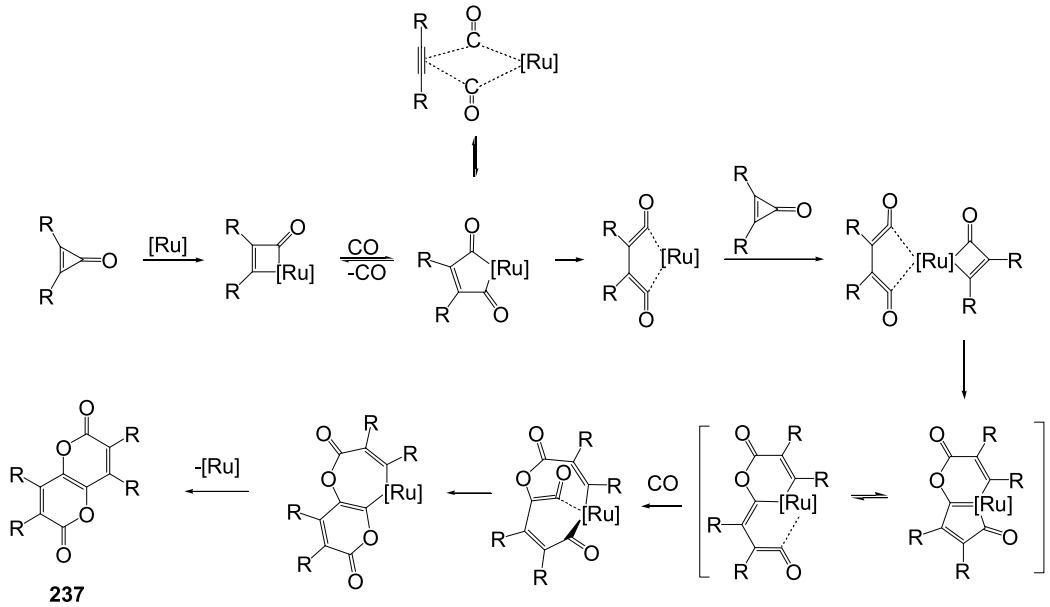


237a-d

Scheme 92. (i) CO (20 atm), $Ru_3(CO)_{12}$ (3.3 mol%), Et_3N (10 mol%), toluene, 150 °C, 20 h. **237**: **a** R=Et, R′=Pr (54%); **b** R=Pr, R′=Bu, (63%); **c** R=Pr, R′=Pen (71%); **d** R=Bu, R′=Pen (82%).

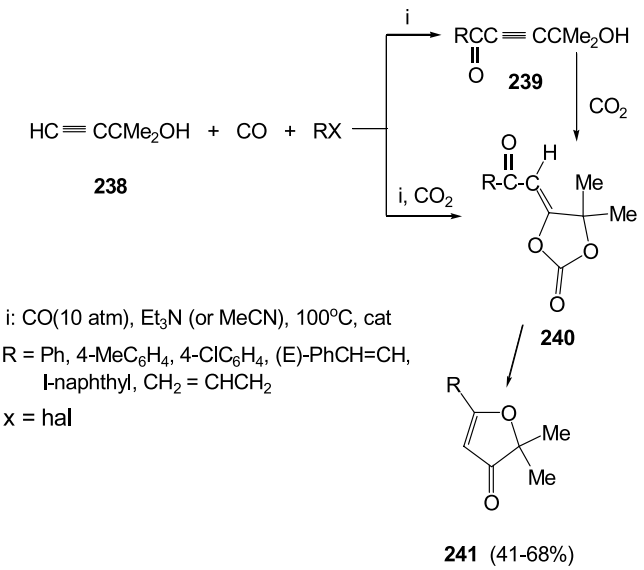
high yields by a novel ruthenium-catalysed cross-carbonylation of cyclopropenones with internal alkynes (Scheme 92).

The use of ^{13}CO gave the corresponding ^{13}C-labelled pyanopyrandiones **237a-d**. The authors believe that the initial step in the present reaction might be consistent with the oxidative addition of the C–C bond between a carbonyl and the α-carbon in cyclopropenone to an active ruthenium centre to give a ruthenacyclobutenone intermediate. Carbonylation of ruthenacyclobutenone (or carbonylative cyclisation of alkynes on the ruthenium) would initially give a malceylruthenium intermediate. Subsequent isomerisation of the maleoylruthenium intermediate produces an active (η^4-bisketene)ruthenium intermediate, which reacts with another molecule of cyclopropenone by oxidative addition and insertion reactions to give a (ketene)ruthenium intermediate. Rapid tautomerisation would give a ruthenium carbene intermediate, and insertion of carbon monoxide into



237

Scheme 93.



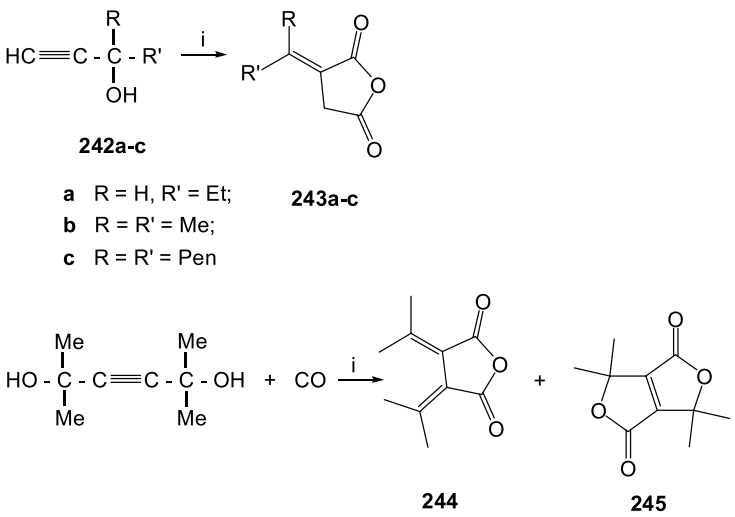
241 (41-68%)

Scheme 94.

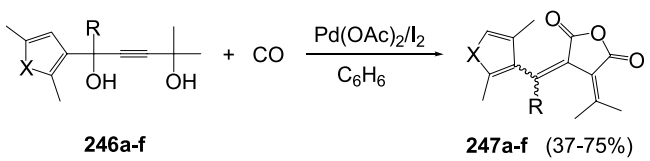
the carbene–ruthenium bond would give a new ketene intermediate. Finally, insertion of a carbonyl group of a ketene moiety into an acyl-ruthenium bond and reductive elimination would give the desired pyranopyrandione **237** (Scheme 93).

33. Synthesis of 3(2*H*)-furanones

When the transition metal triphenylphosphine complexes of Fe, Co, Ni, Ru, Rh, Pt and Pd [the best being $PdCl_2(PPh_3)_2$] were used as catalysts, 3(2H)furanones **241** were formed from 1,1-dimethylprop-2-ynol **238**, CO and RX in a carbon dioxide atmosphere. The reaction mechanism includes the intermediate production of the acetylenic ketones **239**, followed by the formation of the cyclic carbonates **240** from the ketones and CO_2. The compounds **240** can easily decarboxylate quantitatively into the furanones **241**[119] (Scheme 94). The cyclisation of 1-methylprop-2-ynol or prop-2-ynol in a similar manner was unsuccessful.



Scheme 95. (i) $PdCl_2$ (10–20%), benzene, CO (100 atm), 100 °C.



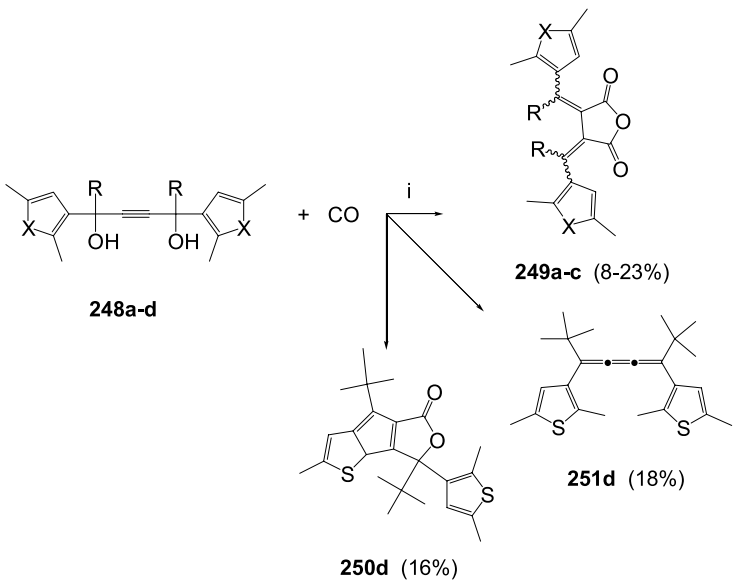
Scheme 96. **a** X=S, R=Me; **b** X=O, R=Me; **c** X=S, R=i-Pr; **d** X=S, R=tBu; **e** X=O, R=iPr; **f** X=O, R=tBu.

34. Cyclic anhydride and imide synthesis

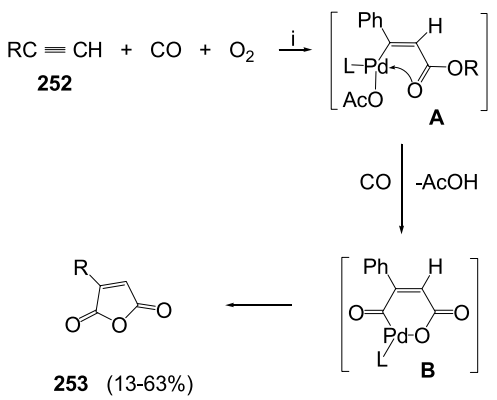
Carbonylation of propargyl alcohol in benzene produced only resinous substances. Substituted propargyl alcohols such as 1-pentyn-3-ol **242a**, 2-methyl-3-butyn-2-ol **242b** and 1-ethynylcyclohexanol **242c** afforded the anhydrides of propylidenesuccinic acid **243a** (19%), teraconic acid **243b** (42%) and cyclohexylidenesuccinic acid **243c** (45%), respectively. The carbonylation of 2,5-dimethyl-3-hexyn-2,5-diol in benzene proceeds smoothly to give the anhydride of diisopropylidenesuccinic acid **244** (49%), as the major product, accompanied by bis(1-hydroxy-1-methylethyl)-furanic acid dilactone **245** (14%) (Scheme 95).[120]

Photochromic anhydrides (fulgides) such as **247** have attracted attention as functional molecules which can be applied to photochemical memory devices.[121] Kiji et al. have proposed a convenient synthetic route to the sterically congested fulgides **247a-f** by the palladium-catalysed carbonylation of heterocycle-substituted 2-butyne-1,4-diol derivatives **246** (Scheme 96).[122,123]

The same authors have applied this method to the synthesis of bisfuryl- or bisthienylfulgides **249a-c** (Scheme 97).[124,125] The diols **248a-c** bearing a methyl or isopropyl group as the alkyl substituent furnished the photochromic fulgides **249a-c**. On the other hand, the carbonylation of the diol bearing a bulky *t*-butyl group **248d** did not afford the corresponding fulgide, but the lactone **250d**, together with butatriene **251d** (Scheme 97).



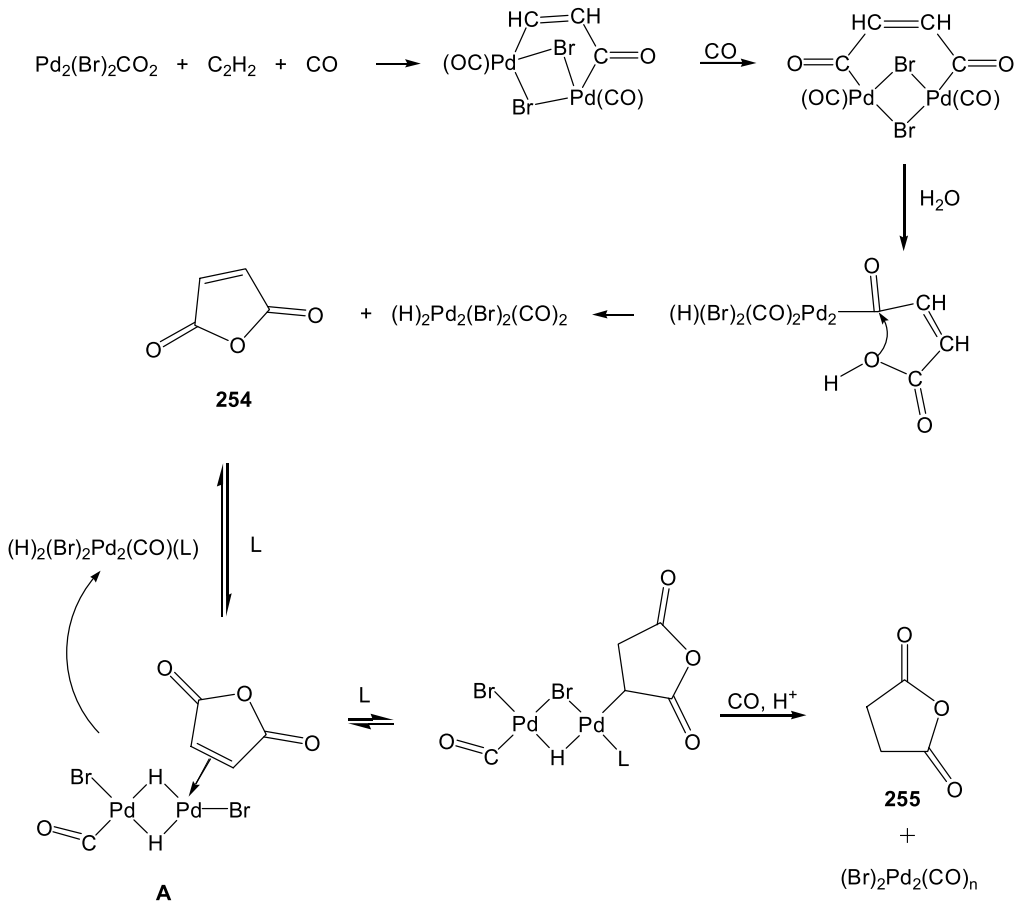
Scheme 97. (i): $Pd(OAc)_2$ (10 mol%), I_2 (5 mol%), benzene, CO (95 atm), 90 °C, 15 h **a** X=S, R=Me; **b** X=O, R=Me; **c** X=S, R=Pr; **d** X=S, R=*t*Bu.



Scheme 98. R=Ph; 4-MeC_6H_4; 4-ClC_6H_4; tBu, Hex, $C_5H_4CH(OH)$. (i) $Pd(OAc)_2$/HQCl/NPMoV, $MeSO_3H$, dioxane, 25 °C, 15 h.

give the corresponding anhydride **253a**. Yamamoto et al. have reported that the carbonylation of 3-butenoic acid with CO by a Pd-complex proceeds through a Pd-containing cyclic intermediate to give the anhydride (Scheme 98).[129]

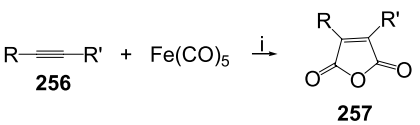
Bruck et al. have shown that the carbonylation of acetylene using the catalytic system $PdBr_2$–LiBr–MeCN produces maleic **254** and succinic **255** anhydrides.[130] A study of the in situ formation of the organic intermediates, the kinetic isotope effect, the isotope exchange, and the oxygen effect on the process direction, revealed that maleic anhydride **254** is most likely a key intermediate in the succinic anhydride **255** formation. Maleic anhydride undergoes transformations through the mediation of a palladium hydride complex **A** (Scheme 99). This complex was detected in the catalytic solution at −40 °C using ^1H NMR techniques.[130]



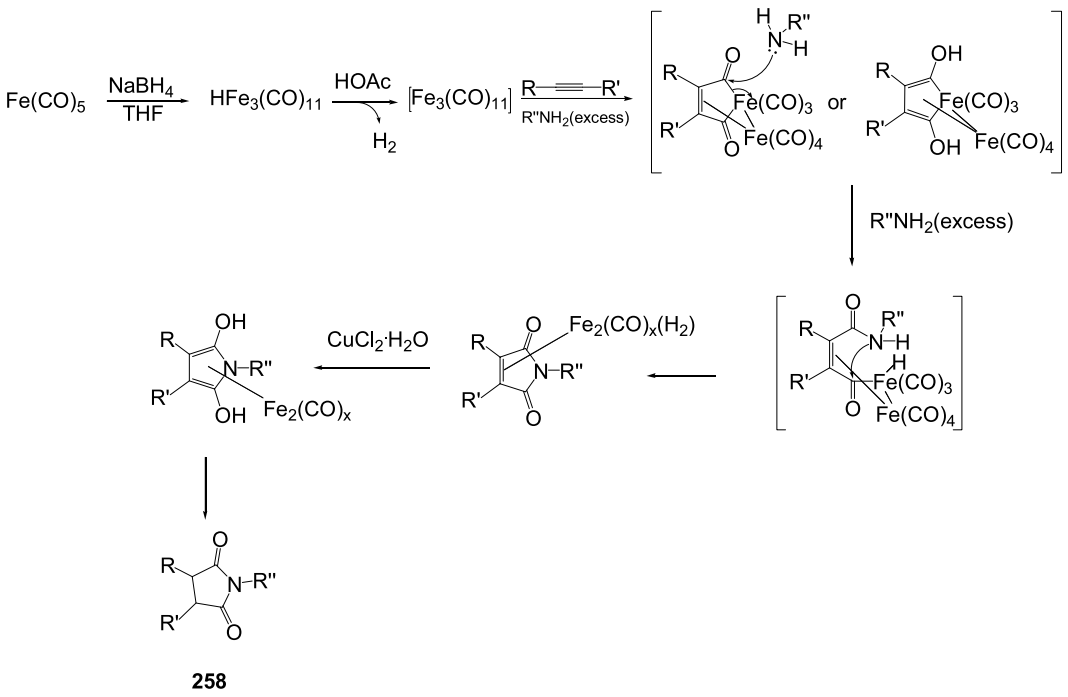
Scheme 99.

The reaction of the alkynes **252** with CO/O_2 in dioxane catalysed by a new triple catalytic system, $PdCl_2$/chlorohydroquinone(HQCI)/NPMoV produced the maleic anhydrides **253** (Scheme 98).[126] The authors[126] consider that the reaction proceeds via a similar mechanism to that shown by Heck[127] for carboalkoxylation and by Alper[128] for dicarbonylation of terminal alkynes. A vinylcarboxylpalladium complex **A** is thought to be a key intermediate in the present carbonylation. When the reaction was performed in dioxane, the insertion of CO into the vinyl complex **A** (R=H) and the elimination of AcOH successively took place to form a palladium complex **B**, which subsequently undergoes reductive elimination to

Periasamy et al.[131] have shown that the reaction of the alkynes **256** with $Fe(CO)_5$ in the presence of pyridine N-oxide (1:1) at 70 °C furnished the corresponding anhydrides **257**, after $CuCl_2.2H_2O$ oxidation (Scheme 100).



Scheme 100. a R=H, R′=Pen (64%), **b** R=H, R′=Ph (58%). (i) (1) Pyridine N-oxide (5 equiv.), $Fe(CO)_5$ (5 equiv.), THF, 67 °C, 12 h; (2) $CuCl_2{\cdot}2H_2O$ (10 equiv.), acetone.



Scheme 101. 258 a R=C_5H_{11}, R′=H, R″=Bu (57%); **b** R=Ph, R′=H, R″=Bu (55%); **c** R=Hex, R′=H, R″=Bu (62%); **d** R=R′=Ph, R″=Bu (55%); **e** R=C(Me)(Ph)OH, r′=Pen, R″=Bu (64%); **f** R=C(OH)Et_2, R′=Pen, R″=Bu, (61%); **g** R=R′=Ph, R″=Oct (53%); **h** R=Pen, R′=H, R″=CH_2Ph (51%).

In addition, the authors have reported[131] that alkyne–iron carbonyl complexes, prepared from $Fe(CO)_5$, $NaBH_4$, HOAC, amine, and alkyne or from $Fe_3(CO)_{12}$, amine and alkyne reagent systems, react with an excess of amine at 25 °C to give the imides **258** in moderate to good yields, after $CuCl_2{\cdot}2H_2O$ oxidation (Scheme 101).

35. Conclusions

This review has discussed new strategies for the synthesis of unsaturated heterocycles, containing nitrogen and oxygen atoms, and carbonyl or alkoxycarbonyl groups in the rings or in the substituents, using catalytic cyclocarbonylation of acetylenic compounds. Heterocycles represent the core of many biologically or pharmaceutically interesting compounds. Acetylene is a multithousand tonne chemical feedstock, which is now mainly produced by the pyrolysis of hydrocarbons. In view of the rapid depletion of hydrocarbon resources, acetylene and its derivatives, which can alternatively be manufactured from coal and other carbon-containing materials, including wastes, are expected to acquire an increasingly more important role as universal chemical intermediates and building blocks. The high and flexible reactivity of these compounds makes the syntheses with their participation easier and less energy consuming than those with alkenes. Nucleophilic attack at the acetylenic moiety leads to diverse vinyl compounds, acetylenic alcohols, allenes, 1,3-dienes and many different heterocycles. The most recent syntheses of functionalised pyrroles, dihydropyridines, quinolines and other fundamental heterocycles by the reaction of carbon monoxide and propargyl derivatives are reviewed. In addition, the recent advances in the modernisation of the classic reactions of acetylene and its derivatives with nucleophiles (superbase-catalysed vinylation of alcohols, polyols or thiols, ethynylation of carbonyl compounds and prototropic rearrangements) are analysed from an up-to-date standpoint. Metal-, mainly palladium-, catalysed reactions serve as versatile tools in synthetic organic chemistry. By using these methodologies, carbon monoxide can be introduced directly into a number of different sites in an organic molecule, leading to the synthesis of carbonyl compounds and carboxylic acid derivatives. The substrate is reacted with a nucleophile such as an alcohol (alkoxycarbonylation), a primary or secondary amine (aminocarbonylation) or water (hydroxycarbonylation) or an organometallic reagent (formylation, cross-coupling reactions) in the presence of carbon monoxide and a palladium complex. Cyclocarbonylation, leading to a variety of heterocyclic compounds, can be regarded as a special type of the former reactions. Double carbonylation usually takes place at elevated CO pressures and produces α-keto-amides or -esters. Cascade reactions may be defined as multireaction, ‘one-pot’ sequences, in which the first reaction creates the functionality to trigger the second. The use of two-phase processes has made catalyst recovery and recirculation, one of the greatest drawbacks of homogeneous catalytic processes, attainable. As palladium-catalysed carbonylations usually tolerate a great variety of functional groups, they are attractive methods for the selective synthesis of intermediates of natural and/or biologically active products.

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Rh(I)-catalyzed solvent-free *ortho*-alkylation of aromatic imines under microwave irradiation

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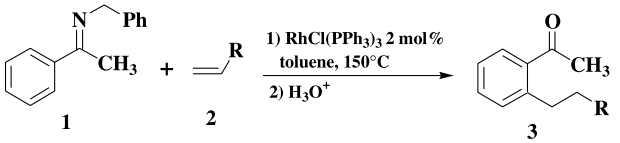
Abstract—The synthesis of *ortho*-alkylated ketones through a chelation-assisted Rh (I) catalyzed *ortho*-alkylation reaction of aromatic imines under microwave activated solvent-free conditions in monomode reactors was performed. These conditions have been also applied to hydroacylation and *ortho*-alkylation reactions with aldimines.

A solvent-free protocol for rhodium (I)-catalyzed intermolecular hydroacylation was achieved using microwave irradiation to produce various ketones in high yields.[1] The reactivity was improved by the addition of aniline as well as 2-amino-3-picoline and benzoic acid to induce a transimination, which facilitated the formation of intermediate aldimines. An accurate comparison between conventional heating mode and microwave irradiation under similar conditions revealed important non-thermal microwave specific effects during chelation-assisted hydroacylation. This effect originated from the imine formation as a result of the condensation of aldehyde and amine.

We have recently developed a rhodium (I)-catalyzed *ortho*-alkylation of ketimines (Eq. (1)).[2]



(1)

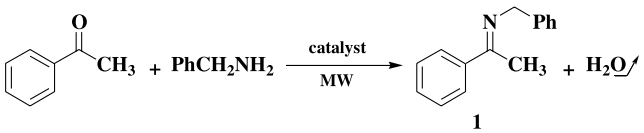
In this reaction, internal olefins and α-ω dienes could be used, contrary to the Ru-catalyzed *ortho*-alkylation of ketones reported by Murai et al.[3,4] where such olefins were not reactive.

In this paper, we describe an improved synthesis of ketimine **1** and its *ortho*-alkylation under solvent-free conditions using microwave irradiation (MW), inside monomode reactors with accurate control of power and temperature.

1. Ketimine preparation

The synthesis of imines from aromatic ketones is far more difficult to achieve than from aldehydes[5] because of imine–enamine isomerisation. Classically, the synthesis of **1** was carried out under conventional conditions in refluxing toluene using a Dean–Stark apparatus with a moderate yield (50%) after 5 days.[6]

A first improvement was reported by Texier–Boullet[7] for the synthesis of **1** on alumina in 'dry media' with a yield of 70% after 7 h at 70 °C. Therefore, taking advantage of MW irradiation under solvent-free conditions[8], we have investigated the reaction in 'dry media' under MW using different acid catalysts (Eq. (2) and Table 1).



(2)

In our hands, using a Synthewave S402 monomode MW reactor with standard vessels, we got a yield of 33% in the reaction with $ZnCl_2$ as catalyst. The water, which was not removed, condensed on the cold walls of the vessels and falling thus in the reaction mixture.

Keywords: Microwave irradiation; *Ortho*-alkylation; Wilkinson catalyst; Solvent-free procedure; Aromatic imines.
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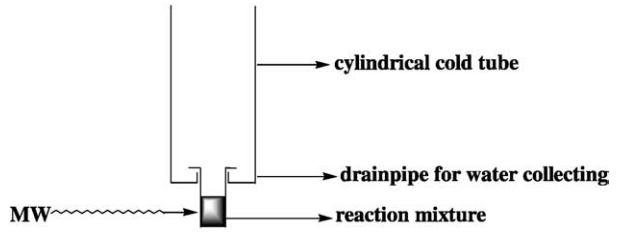
Table 1. MW-assisted synthesis of ketimine **1** using the system depicted in Scheme 1 (1 h, 120 °C)

Additive (10 mol%)	Yield (%)**1**[a]
No catalyst	50
$PhCO_2H$	51
KSF clay	44[b]
TsOH	50
$SnCl_2$	73
$SnCl_2{\cdot}2H_2O$	62
$ZnCl_2$	85
$ZnCl_2{\cdot}4H_2O$	71

[a] GC yield using an internal standard.
[b] 1 h at 150 °C.

In order to shift the equilibrium to the right, the reaction was carried out by using a trapping water system in an open vessel. We thus used a MW equipment with a vessel capable of condensing water on its cold walls (at ambient temperature) and avoiding the water falling inside the reaction mixture. The reagents were mixed together in a pyrex beaker introduced in a cylindrical tube fitted with a drainpipe at the bottom to collect the water (Scheme 1).



Scheme 1. Equipment used for the equilibrium displacement of water under MW irradiation.

Various acid catalysts were tested, and the most significant results are given in Table 1. Apparently, Bronstëd acids are rather inactive whereas Lewis acids led to improvements in yields. The best result (85% yield) was obtained using $ZnCl_2$. The special efficacy of this catalyst in organic synthesis under MW irradiation has already been advocated for the Beckmann rearrangement of benzaldehyde and 2-hydroxyacetophenone oximes,[9] for D-glucose peracetylation, and for decanol glucosylation.[10] It is presumably connected to efficient electrophilic assistance by $ZnCl_2$ due to its complexation to the carbonyl compound.

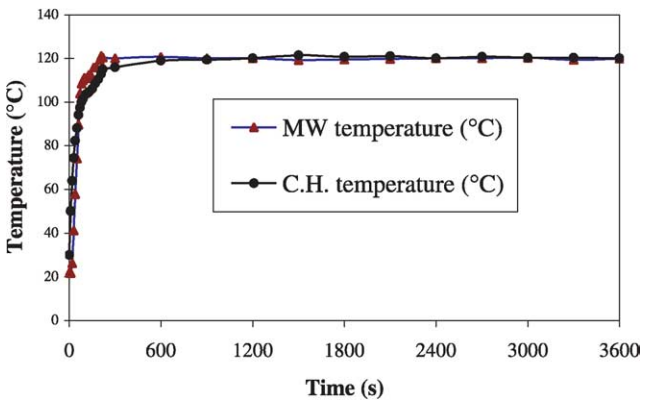
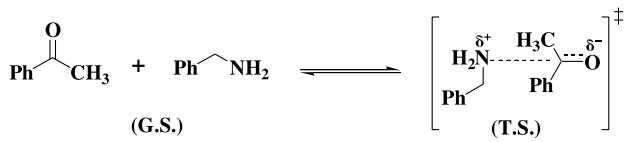


Figure 1. Temperature profiles registered during the $ZnCl_2$ catalyzed synthesis of ketimine **1** under microwave irradiation (MW) and conventional heating (C.H.) at 120 °C (Table 1).

A non-thermal MW specific effect was evident as only a 62% yield was obtained under conventional heating with strictly identical conditions (time, temperature, vessel, mechanical stirring, temperature ramp) (Fig. 1). Under MW irradiation, the temperature was maintained constant at 120 °C by modulation of emitted power between 15 and 300 W. In this case, the main value was about 60 W during the reaction.

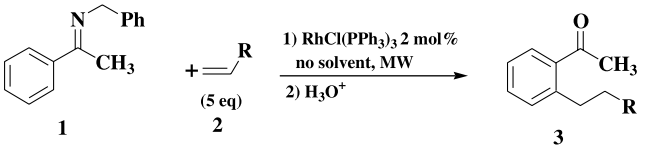
This observation is consistent with mechanistic considerations because the polar mechanism involves a development of charges in the transition state and therefore an increase in the polarity of the system during the course of the reaction. This induces a specific MW enhancement by lowering the activation energy due to a greater stabilisation of the transition state (T.S.) by dipole–dipole interaction with the electric field when compared to the ground state (G.S) (Scheme 2).[11]



Scheme 2. Mechanism of ketimine synthesis.

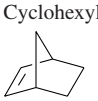
2. Rhodium (I)-catalyzed *ortho*-alkylation

First attempts at solvent-free MW-assisted *ortho*-alkylations were performed using a domestic MW oven. Various olefins were tested and led to the corresponding *ortho*-alkylated ketones after hydrolysis (Eq. (3) and Table 2). Yields obtained under classical conditions (toluene in closed vessels at 150 °C for 2 h) are also indicated in Table 2.



(3)

Table 2. Rh (I)-catalyzed *ortho*-alkylation of ketimine **1** (2 mmol) under MW irradiation (domestic oven, emitted power: 850 W) for 15 min in closed vessels inside Teflon bottles

2, R=	Yield (%) **3**[a]	Yield (%) **3**[2] under classical conditions, 2 h, toluene, 150 °C
t-Bu	98 (93)	97
$SiMe_3$	100 (98)	92
Cyclohexyl	98 (97)	65
	100 (96)	86

[a] Yield estimated by GC using an internal standard (isolated yields are given in brackets).

In order to improve the results (especially when R=*n*-Bu and R=*n*-Oct) and to operate under accurate and controlled conditions including temperature and emitted MW power, significant reactions were performed using a monomode reactor (CEM Discover or Synthewave 402 Prolabo) (Table 3). To check the possible intervention of a non-thermal MW

Table 3. Rh (I)-catalyzed *ortho*-alkylation of ketimine **1** (2 mmol) using monomode MW irradiation in closed vessels (modulation of power between 15 and 300 W)

2, R=	Temperature (°C)	Time (min)	GC yield (%) **3**	
			MW	C.H.
n-Bu	170	90	81 (73)[a]	73
t-Bu	170	60	89	81
n-Oct	170	15	84	78
		60	92	87
	200	15	89 (86)[a]	91

[a] Isolated yields are given in brackets.

specific effect,[11] reactions were performed using a thermostatted oil bath (C.H.=conventional heating) under strictly identical reaction conditions.

Excellent yields were obtained in all cases. Noticeable improvements were evident when using a monomode system rather than a domestic multimode oven.[12]

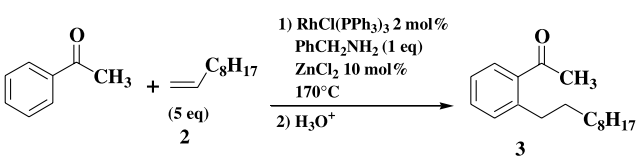
The MW influence here is limited to a purely thermal effect presumably due to wave focusing as expected for a non-polar mechanism where the ground and transition states have rather similar polarities. There was no evidence of special MW effect. The amount of olefin, used initially as a 5-fold excess, could be reduced to 3 equiv. by performing the reaction at 200 °C (Table 4).

Table 4. Effect of the amount of olefins in the *ortho*-alkylation of ketimine **1** using monomode MW irradiation, **2**: R=*n*-Oct

Temperature (°C)	Time (min)	Isolated yield (%) **3**	
		3 equiv.	5 equiv.
170	15	62	78
	60[a]	78	92
200	15[b]	86	89

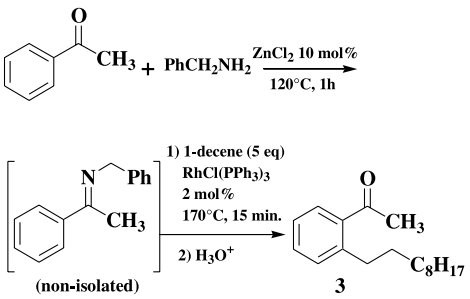
[a] Estimated power=50–80 W.
[b] Estimated power=100 W, pressure=10–25 psi.

We have tried to realise the sequence ketimine preparation/*ortho*-alkylation in a one-pot procedure. Reactions were performed using the CEM Discover system in closed vessels under magnetic stirring for 15 min by mixing all the reagents. We obtained a 43% yield for **3**, which was improved to 56% by extending the reaction time up to 1 h (isolated yield, Eq. (4)).



(4)

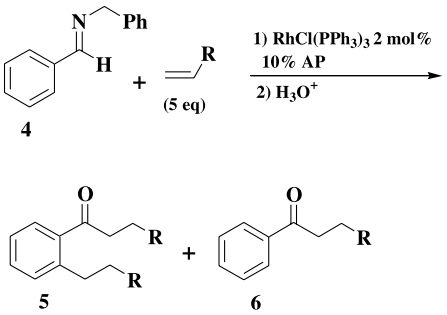
Another attempt involved preparing the ketimine **1** in situ followed by *ortho*-alkylation using 1-decene and Wilkinson's catalyst without ketimine isolation. A 54% yield of **3** was obtained (Eq. (5)).



(5)

In conclusion, the two step procedure with ketimine isolation seems to be preferable giving a satisfactory yield (overall yield 78% with 85 and 92% yields for each step) by comparision to the one-pot procedure (54–56%).

When aldimine was used instead of ketimines in the presence of 2-amino-3-picoline (AP), consecutive hydroacylation and *ortho*-alkylation proceeded at 170 °C under solvent-free conditions.[2] In order to establish the mechanism in the hydroacylation and *ortho*-alkylation, the reaction was studied over the course of time when exposed to MW or conventional heating (CH) under identical reaction conditions (Eq. (6) and Table 5).



(6)

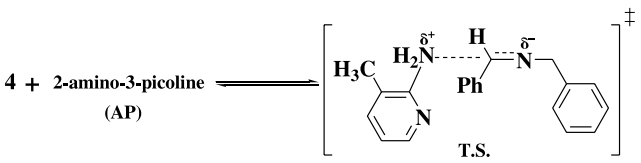
Table 5. Rh (I)-catalyzed reaction of **4** with **2** R=*t*-Bu using monomode MW irradiation in closed vessels

Temperature (°C)	Time (min)	**5/6** (%)	
		MW	C.H.
170	30	40/60	25/61
	60	60/40	64/30
	360		95/5
200	30	96/4	67/21
	60	98/1	81/16

As the use of longer reaction times led to an enhancement in selectivity **5/6** (ex: C.H. for 30 min: 25/61; 60 min: 64/30; 360 min: 95/5), it is clear that hydroacylation proceeds prior to *ortho*-alkylation.

By comparing MW and C.H. activation, appreciable non-thermal MW specific effects are observed especially for short reaction times (30 min at 200 °C, MW: 96/4; C.H.: 67/21).

In order to explain this result, it may be assumed that the initial transimination of aldimine **4** with 2-amino-3-picoline[13] might be the rate determining step. In such a situation, the transition state is expected to be more polar than the



Scheme 3. Mechanism of the transimination of **4** with 2-amino-3-picoline.

ground state due to charge development and therefore more sensitive to MW dipole–dipole stabilisation. Consequently, MW irradiation can accelerate the transimination step by a greater factor than could be achieved by classical means (Scheme 3).[14]

Non-thermal MW specific effects are based in qualitative polarities between ground and transition states. These values have been quantitatively determined by theoretical calculations with the help of Hyperchem 5.1 system. Hessian calculations were carried out after fully location of the transition structures by PM3 semi-empirical method. In fact, the calculated values of the electric dipole moment are: μ=1.23, 1.96 and 6.37 Debyes for the imine **4**, 2-amino-3-picoline and the transiminative transition state, respectively. The values show clearly that the transition state is more polar than the ground state during this transformation as expected. The optimised transition state structure is shown in Figure 2.

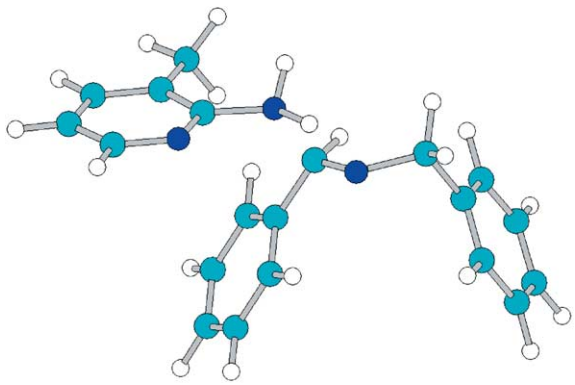


Figure 2. Optimised transition state for transimination of **4** with 2-amino-3-picoline (d_{N-C}: 1.55 Å).

In conclusion, we have developed an efficient procedure for the synthesis of *ortho*-alkylated aromatic ketones through a chelation-assisted Rh (I) catalysed *ortho*-alkylation reaction of aromatic imines using solvent-free reactions and microwave activation under 'green chemistry' conditions. We have also reported on a new method for the synthesis of aromatic imines from aromatic ketones under these conditions. Efforts to extend this method to the preparation of aromatic ketones from 1-alkynes[15] instead of olefins are currently in progress.

3. Experimental section

3.1. Preparation of ketimine 1 and aldimine 4

Acetophenone or benzaldehyde (10 mmol), benzylamine (12 mmol) and zinc chloride (1 mmol) were introduced into a special vessel adapted to the MW reactor and modified to allow water removal (Scheme 1). The reaction mixture was submitted to MW irradiation (monomode system: Synthewave 402 Prolabo or CEM Discover) at 120 °C for 60 min. The temperature is measured by IR detection and controlled by an optical fiber (after calibration of the IR detector). It remains at a constant value by modulation of the emitted power using a computered system. After cooling, the reaction mixture was diluted with diethyl ether and dried over anhydrous $MgSO_4$. After filtration and evaporation, the crude product was purified by distillation under reduced pressure to afford the imine as a colourless liquid. These imines have already been reported in the literature.

3.2. General procedure for *ortho*-alkylation

Imine (2 mmol), alkene (10 mmol), and Wilkinson's catalyst (0.04 mmol) were mixed in the absence of any organic solvent and then exposed to MW irradiation for a certain period of time and at adequate temperature (see Tables 2–4). Two kinds of systems were used, either a domestic oven (Samsung, RE-431H, 700 W) or a monomode reactor (Synthewave 402 Prolabo or CEM Discover) with temperature measurement and power modulation between 15 and 300 W. After cooling, the reaction mixture was extracted using CH_2Cl_2 (3×20 mL). The organic phase was then washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified through flash chromatography (ethyl acetate/pentane=3/7) to afford the corresponding ketone. All products have already been described in the literature.[2]

Acknowledgements

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Synthesis of psudoheliotridane via formal [3+2] annulation and ring-closing metathesis☆,☆☆

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Abstract—Base-induced coupling/cyclization stepwise [3+2] annulation of α-sulfonylacetamide with (*Z*)-2-bromoacrylates yielded polysubstituted pyroglutamates with three contiguous chiral centers with *trans–trans* orientation in a one-pot synthesis. The pyrrolizidine skeleton was obtained via the ring-closing metathesis (RCM) method. This facile strategy was used to synthesize psudoheliotridane.

1. Introduction

Recently, we introduced a new and general methodology for the syntheses of pyroglutamates via [3+2] annulation reactions between different α-sulfonylacetamide derivatives and various ethyl (*Z*)-2-bromo-2-propenoates.[1–4] To demonstrate the synthetic utility of our methodology and continuing our investigation on the application of this methodology to the synthesis of alkaloids, the synthesis of pyrrolizidine alkaloids psudoheliotridane (**1a**) was investigated.[5] Pyrrolizidines and related compounds have attracted considerable attention due to their chemical and pharmacological properties (Fig. 1).

Psudoheliotridane (**1a**) Heliotridane (**1b**)

Figure 1. Structure of psudoheliotridane (**1a**) and heliotridane (**1b**).

2. Results and discussion

2.1. Retrosynthetic approach to psudoheliotridane

Our approach to psudoheliotridane (**1a**) was shown in Scheme 1. We envisioned that the pyrrolizidine skeleton could be achieved via the facile intermolecular [3+2] annulation to pyroglutamate skeleton followed by intramolecular ring-closing metathesis (RCM) with Grubbs' catalyst.

2.2. Synthesis of psudoheliotridane

Allylamine was treated with chloroacetyl chloride and triethylamine to produce α-chloroacetamide, which was then treated with *p*-toluenesulfinic acid sodium salt; the two-step reaction gave α-sulfonylacetamide **3** in 85% yield. Treatment of acetaldehyde with $Ph_3P{=}C(Br)CO_2Et$ gave ethyl (*Z*)-2-bromo-2-butenoate **4** in 98% yield.[6] Compounds **3** and **4** were the reasonable starting materials for the synthesis of pyroglutamate skeleton.

The [3+2] reaction of **3** with **4** (NaH/THF)[1] proceeded smoothly, the cyclized pyroglutamate **5** was obtained as a single isomer in 52% yield in which the substitutents at C_2 and C_3 and C_3 and C_4 are *trans* to each other (Scheme 2). The reaction mechanism for the outstanding stereoselectivity of the annulation reaction has been reported by us.[1–4] The structure of **5** was determined by single-crystal X-ray analysis.[7] With the requisite pyroglutamate **5** in hand, we then examined the reduction of **5**. When **5** was treated with lithium aluminum hydride, **6a** and **6b** were yielded in the ratio of 7:1 with 86% overall yield. However, reaction of **5** with alane reagent [$LiAlH_4/AlCl_3$], only **6b** was produced. Under a milder condition, the reduction of **5** with sodium borohydride gave the desired **6a** as the sole product in 90%

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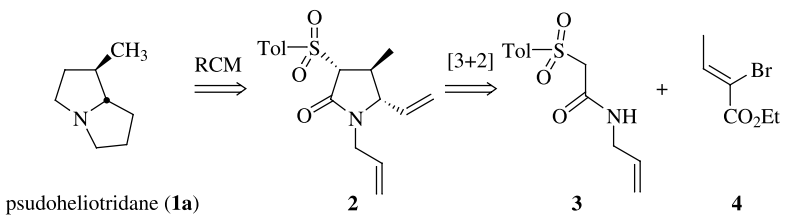
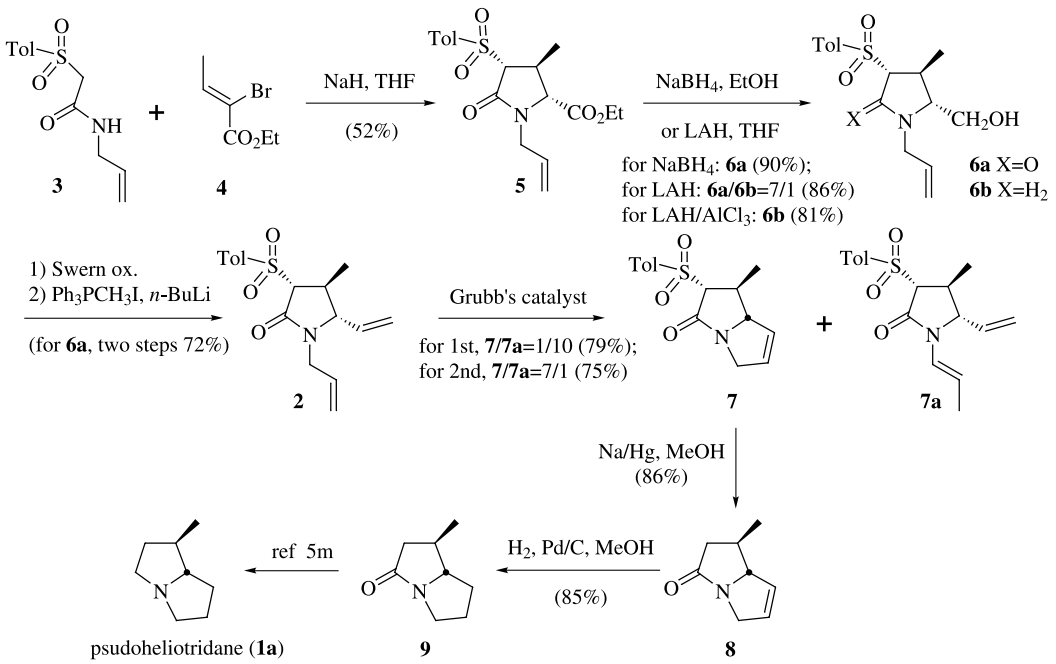


Scheme 1.



Scheme 2.

yield. Preparation of diene **2** was achieved by Swern oxidation of alcohol **6a** followed by Wittig olefination of the resulting aldehyde with methyl triphenylphosphonium iodide. Diene **2** is a reasonable intermediate for the synthesis of psudoheliotridane (**1a**) (Diagram 1).

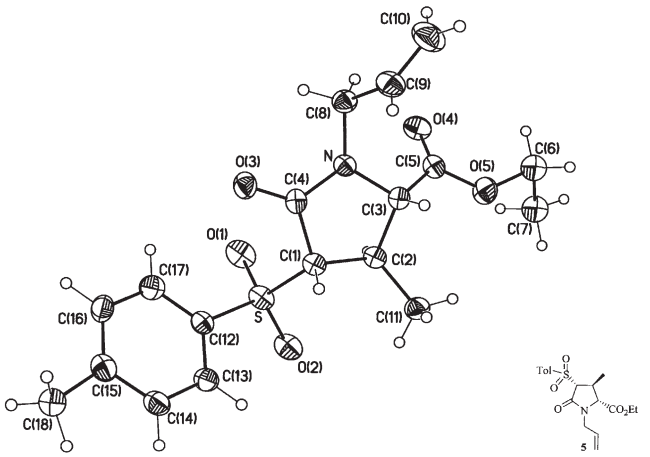


Diagram 1. X-ray crystallography of **5**.

To build up the pyrrolizidine skeleton, diene **2** was subjected to RCM reaction. Ring-closing metathesis (RCM) has been established as a powerful method for the elaboration of medium-sized rings, including carbohydrates, heterocycles and alkaloids.[8,9] In our case, the pivotal issues were the ring strain in the [3.3.0] bicyclic product and the amino group in the pyrrolidine ring that could potentially chelate the metal center of the Grubbs' metathesis catalyst and thus form unproductive complex. When **2** was subjected to a RCM reaction employing first generation Grubbs' catalyst **A** [$Cl_2(PCy_3)_2Ru{=}CHPh$], the expected bicyclic lactam **7** was generated in low yield (Fig. 2).

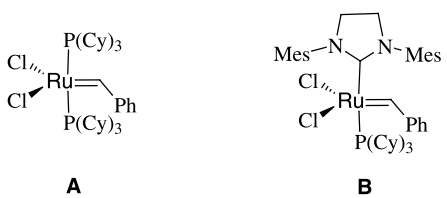


Figure 2. Commercially available Grubbs catalyst **A** and **B**.

During the ring closure process, bis(olefin)-pyroglutamate **2** was affected by catalyst **A**, isomerization of double bond occurred and enamine-olefin **7a** was the major product under a number of conditions (prolonged reaction time, elevated temperature, different solvents). This result was rather surprising because catalyst **A** has been shown tolerant a variety of functional groups, although there have been scattered reports of double bond migration problems with this catalyst.[8,9] The ring strain existed in the desired

5,5-fused product **7** might retard the normally facile cyclization.[8]

We next turn our attention to examine the second generation Grubbs' catalyst **B**, which has higher thermal stability and lower sensitivity to double bond migration. Using similar reaction conditions, compound **7** was obtained as the major product in 65% yield. Finally, desulfonation of **7** was accomplished by treatment of **7** with 6% sodium amalgam (Na/Hg) to give compound **8**. To accomplish the synthesis of psudoheliotridane (**la**), hydrogenation of double bond in **8** was conducted with 10% palladium on carbon.

3. Conclusion

We explored one-pot reaction, using facile intermolecular cycloaddition strategy, to form the pyroglutamate skeleton. Efficient intramolecular ring-closing metathesis (RCM), using the second Grubbs' catalyst **B**, generated pyrrolizidine skeleton. This consecutive cyclization strategy is synthetically useful for constructing pyrrolizidine alkaloids. The formal synthesis of psudoheliotridane (**la**) was accomplished. We are currently studying the scope of this process as well as additional applications of this approach to the synthesis of various pyrrolizidines and indolizidines.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. All reported melting temperatures are uncorrected.

4.1.1. 1-Allyl-2-(4-methylphenylsulfonyl)acetamide (3). Chloroacetyl chloride (1.2 g, 10.6 mmol) in THF (20 mL) was added to a solution of allylamine (0.57 g, 10.0 mmol) and triethylamine (1.06 g, 10.5 mmol) in THF (30 mL) in an ice bath for 30 min, then stirred at rt for 4 h. The mixture was concentrated under reduced pressure. Water (30 mL) was added to the crude product and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Without purification, the crude product with *p*-toluenesulfinic acid sodium salt (3.2 g, 16.5 mmol) was refluxed in dioxane (70 mL) and water (70 mL) for 15 h. The mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (2×20 mL), dried, filtered and evaporated. Recrystallization on hexane (60 mL) and ethyl acetate (30 mL) yielded **3** (2.15 g, 85%): mp 136–137 °C (hexane/ethyl acetate); EI-MS: $C_{12}H_{15}NO_3S$ *m/z* (%)=98 (100), 253 (M^+, 1); HRMS (EI, M^+) Calcd for $C_{12}H_{15}NO_3S$ 253.0773, found 253.0770; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 6.90 (br s, 1H), 5.82–5.73 (m, 1H), 5.24–5.12 (m, 2H), 4.00 (s, 2H), 3.86–3.83 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.60, 145.64, 135.29, 133.10, 130.05 (2×), 128.18 (2×), 117.00, 62.06, 42.34, 21.66. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.72; H, 6.04; N, 5.58.

4.1.2. Ethyl 2-bromo-2-buteoate (4).[6] A solution of acetaldehyde (1.32 g, 30.0 mmol) in DCM (10 mL) was added to a rapidly stirred solution of $Ph_3P{=}C(Br)CO_2Et$ (13.2 g, 3.1 mmol) in DCM (40 mL), then stirred at rt for 7 h. The resulting mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue, and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (40/1–20/1) produced **4** (585 mg, 98%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (q, *J*=6.0 Hz, 1H), 4.27 (q, *J*=6.0 Hz, 2H), 1.94 (d, *J*=6.0 Hz, 3H), 1.32 (t, *J*=6.0 Hz, 3H).

4.1.3. Ethyl 1-allyl-3-methyl-4-(4-methylphenylsulfonyl)pyroglutamate (5). A solution of **3** (253 mg, 1.0 mmol) in THF (30 mL) was carefully added to a rapidly stirred suspension of sodium hydride (1.24 g, 3.1 mmol, 60%) in THF (30 mL). After the reaction mixture was stirred at rt for 15 min, a solution of **4** (212 mg, 1.1 mmol) in THF (30 mL) was added. The resulting mixture was stirred for 6 h at refluxed temperature, quenched with saturated ammonium chloride solution (2 mL) in an ice bath, and concentrated under reduced pressure. Water (20 mL) was added to the crude product, and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (4/1–2/1–1/1) produced **5** (190 mg, 52%): mp 101–103 °C; FAB-MS: $C_{18}H_{23}NO_5S$ *m/z* (%)=136 (100), 154 (28), 210 (10), 366 (M^++1, 45); HRMS (FAB, M^++1) Calcd for $C_{18}H_{24}NO_5S$ 366.1375, found 366.1373; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J*=8.0 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 5.65–5.57 (m, 1H), 5.20–5.12 (m, 2H), 4.42 (dd, *J*=5.0, 15.0 Hz, 1H), 4.31–4.18 (m, 2H), 3.70 (d, *J*=4.5 Hz, 1H), 3.62 (dd, *J*=8.0, 15.0 Hz, 1H), 3.60 (d, *J*=5.5 Hz, 1H), 3.21–3.14 (m, 1H), 2.44 (s, 3H), 1.42 (d, *J*=7.5 Hz, 3H), 1.32 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.46, 164.94, 145.29, 134.37, 130.78, 129.54 (2×), 129.42 (2×) 119.72, 71.72, 63.69, 61.79, 44.92, 32.59, 21.67, 20.79, 14.07. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 59.41; H, 6.24; N, 3.80.

Single-crystal X-ray diagram:[7] crystal of **5** was grown by slow diffusion of ethyl acetate into a solution of **5** in DCM to yield colorless prism. The compound crystallizes in the orthorhombic crystal system, space group. *Pca*2(1), *a*=9.8102(11) Å, *b*=10.3120(12) Å, *c*=18.686(2) Å, *V*=1890.3(4) Å^3, *Z*=4, d_{Calcd}=1.284 mg/m^3, absorption coefficient 0.198 mm^{-1}, *F*(000)=776, 2θ range (1.97–26.04°).

4.1.4. 1-Allyl-5-hydroxymethyl-4-methyl-3-(4-methylphenylsulfonyl)pyrrolidin-2-one (6a) and 1-allyl-3-methyl-4-(4-methylphenylsulfonyl)prolinol (6b). For

$NaBH_4$ condition: a solution of **5** (310 mg, 0.85 mmol) in ethanol (10 mL) was stirred at rt, and sodium borohydride (150 mg, 4.0 mmol) and lithium chloride (170 mg, 4.0 mmol) was added. The mixture was stirred for 12 h at rt. Saturated sodium bicarbonate solution (1 mL) was added to the mixture and the mixture was concentrated under reduced pressure. Water (1 mL) was added to the residue, and the mixture was extracted with DCM (3×10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (2/1–1/1) produced **6a** (247 mg, 90%).

For LAH condition: a solution of **5** (310 mg, 0.85 mmol) in THF (20 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) and the resulting reaction mixture was stirred for 2 h, then quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3×20 mL). The organic layers were washed with brine, dried, filtered and evaporated. Purification of the crude product by column chromatography on silica gel with hexane/ethyl acetate (2/1–1/1) produced **6a** (206 mg, 75%) and **6b** (29 mg, 11%).

For alane condition: a solution of **5** (310 mg, 0.85 mmol in THF (10 mL) was added to a solution of lithium aluminum hydride (57 mg, 1.5 mmol) and aluminum chloride (214 mg, 1.6 mmol) in THF (10 mL) via syringe at 0 °C. The mixture was refluxed for 2 h at rt, quenched with saturated ammonium chloride solution (1 mL) under cooling, and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude compound. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **6b**.

For **6a**: gum; FAB-MS: $C_{16}H_{21}NO_4S$ *m/z* (%)=136 (71), 154 (63), 324 (M^++1, 100); HRMS (FAB, M^++1) Calcd for $C_{16}H_{22}NO_4S$ 324.1269, found 324.1270; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J*=8.5 Hz, 2H), 7.37 (d, *J*=8.5 Hz, 2H), 5.75–5.67 (m, 1H), 5.22–5.18 (m, 2H), 4.12 (dd, *J*=5.5, 15.5 Hz, 1H), 3.84–3.73 (m, 3H), 3.62 (d, *J*=6.0 Hz, 1H), 3.23 (q, *J*=4.5 Hz, 1H), 2.97–2.90 (m, 1H), 2.45 (s, 3H), 2.18 (br s, 1H), 1.33 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.34, 145.32, 134.60, 131.91, 129.58 (2×), 129.47 (2×), 118.36, 72.29, 64.62, 61.85, 44.32, 30.16, 21.72, 20.70. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.66; H, 6.32; N, 4.40.

For **6b**: gum; FAB-MS: $C_{16}H_{23}NO_3S$ *m/z* (%)=122 (100), 154 (59), 278 (32), 310 (M^++1, 99); HRMS (FAB, M^++1) Calcd for $C_{16}H_{24}NO_3S$ 310.1477, found 310.1476; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.0 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 5.79–5.71 (m, 1H), 5.21–5.14 (m, 2H), 3.69 (dd, *J*=3.0, 11.5 Hz, 1H), 3.60 (dd, *J*=3.0, 11.5 Hz, 1H), 3.42 (d, *J*=11.5 Hz, 1H), 3.37 (dd, *J*=4.5, 13.5 Hz, 1H), 3.20–3.16 (m, 1H), 2.72–2.60 (m, 3H), 2.48–2.44 (m, 1H), 2.46 (s, 3H), 2.17 (br s, 1H), 1.00 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.93, 134.68, 133.88, 129.80 (2×), 129.15 (2×), 118.21, 71.98, 68.21, 57.56, 55.18, 52.95, 35.91, 21.66, 18.04. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 61.91; H, 7.32; N, 4.55.

4.1.5. 1-Allyl-4-methyl-3-(4-methylphenylsulfonyl)-5-vinyl-pyrrolidin-2-one (2). A solution of oxalyl chloride (0.14 mL, 1.56 mmol) in DCM (10 mL) at −78 °C, and dimethyl sulfoxide (0.19 mL, 2.67 mmol) were added carefully. The solution was warmed to −40 °C for 5 min and recooled to −78 °C, and then a solution of alcohol **6a** (160 mg, 0.5 mmol) in DCM (5 mL) was added dropwise for 40 min followed by excess triethylamine (4 mL) for 30 min. The reaction mixture was warmed to rt and poured into saturated aqueous ammonium chloride solution (2 mL), and concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and evaporated to give the crude aldehyde product: FAB-MS: $C_{17}H_{21}NO_3S$ *m/z* (%)=136 (100), 154 (41), 219 (11), 320 (M^+−1, 63), 322 (M^++1, 20); HRMS (FAB, M^++1) Calcd for $C_{16}H_{20}NO_4S$ 322.1113, found 322.1111; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (d, *J*=3.0 Hz, 1H), 7.78 (d, *J*=9.0 Hz, 2H), 7.35 (d, *J*=9.0 Hz, 2H), 5.74–5.66 (m, 1H), 5.25–5.15 (m, 2H), 4.20–4.05 (m, 1H), 3.93–3.83 (m, 1H), 3.58 (d, *J*=3.0 Hz, 1H), 3.50–3.40 (m, 1H), 3.06–2.93 (m, 1H), 2.43 (s, 3H), 1.35 (d, *J*=6.0 Hz, 3H). To a stirred solution of methyl triphenylphosphonium iodide (808 mg, 2.0 mmol) in THF (50 mL) was added *n*-butyllithium (1.0 mL, 1.6 M, 1.6 mmol) and hexamethylphosphoric triamide (HMPA, 0.4 mL) at −78 °C. The orange red colored mixture was stirred at −78 °C for 1 h. The resulting aldehyde product was added to the reaction mixture at −78 °C via a syringe and further stirred at −78 °C for 2 h. The reaction was quenched with aqueous saturated ammonium chloride (10 mL) and the mixture was extracted with diethyl ether (3×50 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=2/1) produced compound **2** (114 mg, 72%): gum; FAB-MS: $C_{17}H_{21}NO_3S$ *m/z* (%)=136 (36), 219 (13), 320 (M^++1, 100); HRMS (FAB, M^++1) Calcd for $C_{17}H_{22}NO_3S$ 320.1322, found 320.1320; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 2H), 5.69–5.55 (m, 2H), 5.33–5.28 (m, 2H), 5.18–5.05 (m, 2H), 4.13 (dd, *J*=4.5, 15.0 Hz, 1H), 3.64 (d, *J*=8.0 Hz, 1H), 3.49–3.43 (m, 2H), 2.75–2.68 (m, 1H), 2.44 (s, 3H), 1.33 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.90, 145.11, 136.05, 134.98, 131.11, 129.54 (2×), 129.48 (2x), 120.70, 118.47, 71.60, 66.85, 43.64, 34.61, 21.69, 18.53. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.68; H, 6.57; N, 4.47.

4.1.6. 1-Methyl-2-(4-methylphenylsulfonyl)-1,2,5,7a-tetrahydro-pyrrolizin-3-one (7) and 4-methyl-1-propenyl-3-(4-methylphenylsulfonyl)-5-vinyl-pyrrolidin-2-one (7a). 1st or 2nd Grubbs' catalyst (0.01 mmol) was added to a solution of **2** (32 mg, 0.1 mmol) in 1,2-dichloroethane (3 mL) and the reaction mixture was refluxed under nitrogen atmosphere for 36 h. The mixture was concentrated and purified by flash column chromatography (hexane/ethyl acetate=2/1–1/1) to yield **7** and **7a**. For Grubb's 1st generation catalyst, the yield: **7** (2 mg, 7%) and **7a** (23 mg, 72%); For Grubb's 2nd generation catalyst, the yield: **7** (21 mg, 66%) and **7a** (3 mg, 9%).

For **7**: gum; FAB-MS: $C_{15}H_{17}NO_3S$ *m/z* (%)=136 (100), 154 (94), 242 (3), 292 (M^++1, 78); HRMS (FAB, M^++1) Calcd for $C_{15}H_{18}NO_3S$ 292.1008, found 292.1007; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H), 5.94–5.88 (m, 2H), 4.37–4.32 (m, 1H), 4.13–4.11 (m, 1H), 3.98 (d, *J*=11.5 Hz, 1H), 3.67–3.62 (m, 1H), 2,82–2.77 (m, 1H), 2.45 (s, 3H), 1.47 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.55, 145.01, 135.28, 129.84 (2×), 129.71 (2×), 120.11, 111.72, 72.95, 71.26, 50.58, 40.50, 21.69, 17.92.

For **7a**: mp 113–114 °C; EI-MS: $C_{17}H_{21}NO_3S$ *m/z* (%)=69 (77), 91 (100), 164 (78), 319 (M^+, 2); HRMS (EI, M^+) Calcd for $C_{17}H_{21}NO_3S$ 319.1237, found 319.1236; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J*=8.5 Hz, 2H), 7.35 (d, *J*=8.5 Hz, 2H), 6.59 (dd, *J*=1.5, 14.5 Hz, 1H), 5.79–5.72 (m, 1H), 5.30–5.23 (m, 3H), 3.74 (dd, *J*=4.6, 8.5 Hz, 1H), 3.64 (d, *J*=6.0 Hz, 1H), 2.75–2.69 (m, 1H), 2.44 (s, 3H), 1.64 (dd, *J*=1.5, 7.0 Hz, 3H), 1.32 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.99, 145.21, 137.62, 134.70, 129.53 (2x), 129.42 (2x), 123.26, 118.07, 111.83, 72.04, 66.58, 34.83, 21.65, 19.61, 15.50. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.76; H, 6.54; N, 4.44.

4.1.7. 1-Methyl-1,2,5,7a-tetrahydro-pyrrolizin-3-one (8). 6% Sodium amalgam (Na/Hg, 0.5 g) and sodium phosphate (71 mg, 0.5 mmol) were added to a stirred solution of **7** (30 mg, 0.1 mmol) in methanol (5 mL), and vigorously stirred for 2 h at rt. The residue was filtered and washed with methanol (2×10 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **8** (12 mg, 86%): oil; HRMS (EI, M^+) Calcd for $C_8H_{11}NO$ 137.0841, found 137.0841; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.92–5.83 (m, 2H), 4.41–4.32 (m, 1H), 4.22–4.14 (m, 1H), 3.70–3.61 (m, 1H), 2.32–2.15 (m, 2H), 1.82–1.72 (m, 1H), 1.22 (d, *J*=7.5 Hz, 3H).

4.1.8. 1-Methyl-hexahydro-pyrrolizin-3-one (9).[5e,g,m,p] 10% Palladium on activated carbon (10 mg) was added to the solution of **8** (7 mg, 0.05 mmol) in methanol (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was continued to stir for 3 h at rt. The catalyst was filtered through a short plug of Celite and washing with methanol (2×5 mL). The combined organic layers were evaporated. Purification on silica gel (hexane/ethyl acetate=1/1–1/2) produced **9** (6 mg, 85%). The ^{1}H NMR data was in accordance with the reported in the literature.

5. Supplementary Material

Experimental procedures and photocopies of ^{1}H-NMR ($CDCl_3$) spectral data for **2**, **5**, **6a**, **6b**, **7**, **7a**, **8** were supported.

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Synthesis of imidazolidin-4-one and 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione derivatives of primaquine: scope and limitations

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Abstract—The synthesis of imidazolidin-4-one derivatives of primaquine as potential antimalarial agents is described. The target compounds were synthesized in three steps: (i) condensation of (±)-primaquine with N^{α}-protected amino acids, (ii) removal of the N^{α}-protecting group, and (iii) reaction of the N-acylprimaquine with a carbonyl compound: acetone, three cyclic ketones and veratraldehyde. Using 2-formylbenzoic acid in the third step afforded 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones. All products were isolated in good to excellent yields. Whereas imidazolidin-4-ones were formed as mixtures of all possible diastereomers in equal amounts, 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones were produced in a stereoselective fashion. The compounds hydrolyse very slowly ($t_{1/2}$ 5–30 d) in pH 7.4 buffer to release primaquine. These primaquine derivatives are being submitted to biological assays, and preliminary results of their antimalarial activity are quite encouraging.

1. Introduction

Primaquine, **1**, is the only currently available drug that is active against both the latent liver forms of the relapsing malaria caused by *Plasmodium vivax* and *Plasmodium ovale*[1] and the gametocytes from all species of parasite causing human malaria, including chloroquine-resistant *Plasmodium falciparum*.[2] However, the clinical use of primaquine is impaired as a result of a rapid metabolic inactivation to form carboxyprimaquine **2**,[3–6] and to serious blood toxicity, particularly the ability to induce oxidation of oxyhemoglobin to methemoglobin.[7] Several peptide and amino acid derivatives of primaquine, for example, **3**, have been prepared to reduce toxicity of the parent as well as to reduce the oxidative deamination metabolic pathway leading to **2**.[8–11] Despite the improved activity/toxicity ratio usually displayed by **3**, most of these derivatives are rapidly hydrolysed to primaquine by aminopeptidases and endopeptidases,[11,12] suggesting that they might undergo extensive hydrolysis to the parent drug in the intestinal lumen when given orally. Thus, the design of orally effective and metabolically stable derivatives of the antimalarial agents **3** is of obvious interest.

Replacement of an amide bond with appropriate isosteres is a commonly used lead-optimization strategy for enhancing enzymatic stability of a peptide.[13] Alternatively, the peptide drug can be converted into a prodrug or transport form that

Keywords: Antimalarial; Imidazolidin-4-one; 1*H*-Imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones; Malaria; Primaquine; Stereoselectivity.

Abbreviations: AA, amino acid; HAAPQ, amino acid derivative of primaquine (unprotected); Ala, alanine residue; Boc, *tert*-butyloxycarbonyl (protecting group); BocAAOH, N^{α}-Boc-protected amino acid; BocAAPQ, N^{α}-Boc-protected amino acid derivative of primaquine; bs, broad singlet; Bzl, benzyl; $CDCl_3$, deuterated chloroform; d, doublet; dd, double doublet; dt, double triplet; δ, chemical shift (in ppm); DCCI, N,N′-dicyclohexylcarbodiimide; DCM, dichloromethane; DCU, N,N′-dicyclohexylurea; DHB, 2,5-dihydroxybenzoic acid; DIEA, diisopropylethylamine; DIPCDI, N,N′-diisopropylcarbodiimide; DIU, N,N′-diisopropylurea; Gly, glycine residue; HOBt, N-hydroxybenzotriazole; ^{t}Bu, *iso*butyl; ^{i}Pr, *iso*propyl; Leu, leucine residue; m, unresolved multiplet; MALDI-TOF, matrix-assisted laser desorption ionization—time-of-flight; NOE, nuclear Overhauser effect; PES, potential energy surface; Phe, phenylalanine residue; ppm, parts per million (NMR chemical shift unit); PQ, primaquine; q, quartet; s, singlet; t, triplet; TEA, triethylamine; THF, tetrahydrofuran; TLC, thin layer chromatography; TMS, tetramethylsilane; Val, valine residue.

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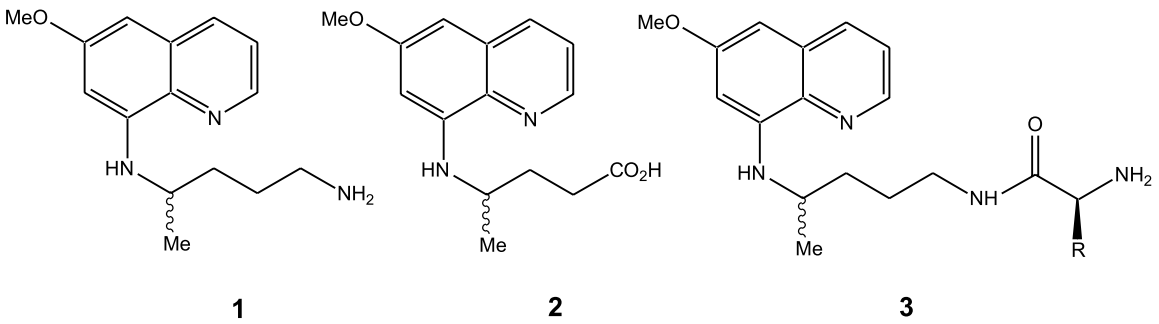
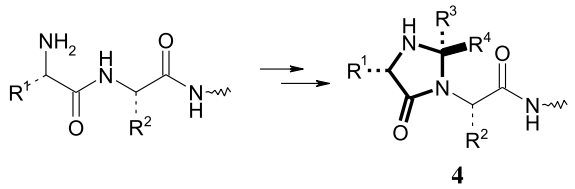


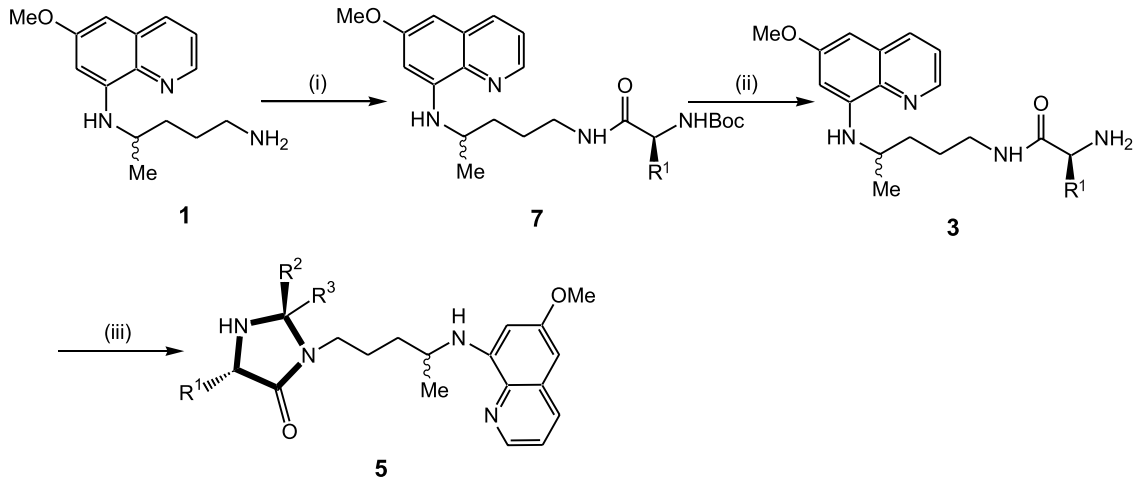
1 **2** **3**



4

Scheme 1.

protects the parent peptide against proteolytic degradation at the mucosal absorption barrier or in the blood.[14] Such a prodrug must be capable of reverting to the parent peptide drug following oral absorption via an unspecific plasma enzyme-catalysed reaction or a non-enzymatic pathway. Imidazolidin-4-one, **4**, formation was introduced as a useful prodrug approach to protect the *N*-terminal amino acid residue of di-, tri- and pentapeptides against



1 **7** **3**

5

Compound	R^1	R^2	R^3	Yield (%)
5a	H	Me	Me	74
5b	Me	Me	Me	81
5c	$CHMe_2$	Me	Me	76
5d	CH_2CHMe_2	Me	Me	62
5e	CH_2Ph	Me	Me	52
5f	H	$-(CH_2)_4-$		50
5g	Me	$-(CH_2)_4-$		61
5h	$CHMe_2$	$-(CH_2)_4-$		55
5i	CH_2CHMe_2	$-(CH_2)_4-$		54
5j	CH_2Ph	$-(CH_2)_4-$		59
5k	H	$-(CH_2)_5-$		75
5l	Me	$-(CH_2)_5-$		69
5m	$CHMe_2$	$-(CH_2)_5-$		62
5n	CH_2CHMe_2	$-(CH_2)_5-$		66
5o	CH_2Ph	$-(CH_2)_5-$		69
5p	H	$-(CH_2)_6-$		52
5q	Me	$-(CH_2)_6-$		44
5r	$CHMe_2$	$-(CH_2)_6-$		48
5s	CH_2CHMe_2	$-(CH_2)_6-$		55
5t	CH_2Ph	$-(CH_2)_6-$		59
5u	Me	3,4-$(MeO)_2$-C_6H_3	H	78[a]
5w	$CHMe_2$	3,4-$(MeO)_2$-C_6H_3	H	85[a]
5y	CH_2CHMe_2	3,4-$(MeO)_2$-C_6H_3	H	57[a]
5x	CH_2Ph	3,4-$(MeO)_2$-C_6H_3	H	94[a]

[a] Total yield corresponding to the sum of all fractions isolated by column chromatography

Scheme 2. (i) DCCI, HOBt, BocAAOH; (ii) (1) TFA, (2) Na_2CO_3; (iii) Me_2CO or C_5, C_6 or C_7 cyclic ketones or 3,4-$(MeO)_2-C_6H_3CHO$ in refluxing MeOH, TEA, molecular sieves.

aminopeptidase-catalysed hydrolysis (Scheme 1).[15–18] The synthetic approaches for the preparation of imidazolidin-4-ones involve the reaction of the peptide with an aldehyde or ketone followed by intramolecular cyclization. This reaction is catalysed by acids[19] or bases[20] although no catalyst is needed with acetone.[21] Usually, peptide imidazolidin-4-one derivatives, **4**, were quantitatively hydrolysed to the parent peptide in physiological conditions (pH 7.4 buffer at 37 °C) with half-lives ranging from in 1 to 30 h, depending on the *N*-terminal dipeptide sequence and on the R^3, R^4 imidazolidinone substituents (Scheme 1).[15–18] The same imidazolidin-4-one strategy was used to improve the bioavailability of ampicillin, a β-lactam that also contains a peptide backbone.[22] The corresponding imidazolidin-4-one, hetacillin, is also rapidly hydrolysed to ampicillin in physiological conditions.

Here we report the synthesis of compounds **5**, incorporating the imidazolidin-4-one scaffold, as potential peptidase-stable prodrugs of amino acid derivatives of primaquine, **3** (Scheme 2). As the primaquine starting material was a racemate, the cyclization reactions of **3** with ketones or aldehydes yielded compounds **5** as the corresponding diastereomeric mixtures. Reaction of **3** with 2-formylbenzoic acid leads to 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione production, **6**, via a diastereoselective cyclization (Scheme 3).

2. Results and discussion

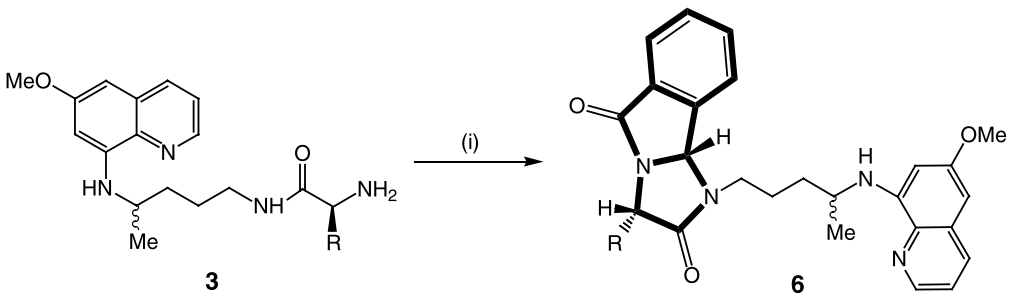
2.1. Synthesis of *N*-α-aminoacylprimaquine derivatives

The target imidazolidin-4-ones **5** were synthesised via the corresponding amino acid derivatives **3** (Scheme 2). The Boc-protected amino acid intermediates **7** were prepared using standard peptide coupling methods[23] that involved N^{α}-Boc protected amino acid (BocAAOH) coupling to (±)-primaquine (PQ), using either dicyclohexylcarbodiimide (DCCI)[24] or diisopropylcarbodiimide (DIPCDI)[25] in combination with the auxiliary nucleophile 1-hydroxybenzotriazole (HOBt).[26] Products **7b–e** were isolated as mixtures of the two possible diastereomers (^{13}C NMR signal duplications were observed), even though they could not be distinguished by the chromatographic techniques employed. The N^{α}-Boc-protected amino acid derivatives of primaquine, **7a–e**, were treated with neat trifluoroacetic acid (TFA) to remove the Boc-protecting group.[27] After neutralization of the resulting trifluoroacetates with aqueous sodium carbonate, the deprotected amino acid derivatives of primaquine (HAAPQ, **3**) were extracted with chloroform and isolated as yellow-orange waxy oils in 83–97% yields. All HAAPQ derivatives, **3a–e**, were characterized by NMR and MALDI-TOF-MS.

2.2. Reaction of the *N*-α-aminoacylprimaquine derivatives with carbonyl compounds

The HAAPQ intermediates, **3a–e**, reacted with acetone, cyclopentanone, cyclohexanone and cycloheptanone, by refluxing both reactants in methanol in the presence of triethylamine (TEA), 4 Å molecular sieves and an excess of the ketone, to form the expected imidazolidin-4-ones, **5**, in good yields (44–81%). When the reaction of **3** with ketones was carried out without TEA or 4 Å molecular sieves (or both) only small amounts of condensation products **5** were isolated. The imidazolidin-4-ones **5**, containing a chiral amino acid residue (e.g., **5b–e**, derived from Ala, Val, Leu and Phe, respectively) were isolated as mixtures of two co-eluting diastereomers, as detected by the duplication of some ^{13}C NMR signals. For example, compound **5c** derived from HValPQ, **3c**, and acetone presented two signals for the following resonances: C-2, C-5 and C-6 in the quinoline ring; C-1′, C-2′, C-3′ and C-4′ in the amine side-chain; C-2 and C-4 in the imidazolidin-4-one ring.

All HAAPQ derivatives, **3**, were also reacted with formaldehyde and ethyl glyoxylate, but, unfortunately,



3 **6**

Compound	R	Yield (%)
6a	H	56
6b	Me	53
6c	$CHMe_2$	59
6d	CH_2CHMe_2	44
6e	CH_2Ph	60

Scheme 3. (i) 2-CHO–$C_6H_4CO_2H$ in refluxing MeOH, TEA, molecular sieves.

only untractable mixtures were obtained. In constrast, reaction of compounds **3b**–**e** with veratraldehyde (3,4-dimethoxybenzaldehyde) as described above, afforded the corresponding imidazolidin-4-ones **5u**–**x** with global yields of 57–94%. The imidazolidin-4-one derived from HGlyPQ, **3a**, was probably formed, since the correct molecular weight was detected by MALDI-TOF-MS analysis of the crude mixture. However, this compound was too unstable to be satisfactorily isolated and characterized by NMR.

The cyclization of **3b**–**e** with aldehydes generates a new chiral centre, so four imidazolidin-4-one diastereomeric pairs are to be expected. In fact, TLC monitoring could distinguish one to four spots in the reaction of veratraldehyde with compounds **3b**–**e**. The closeness between the R_f values for the different diastereomers was obviously high, depending on the amino acid involved. Best chromatographic resolution was found for the Phe-derived product **5x** (all four spots, though close, could be distinguished), whereas for the Leu-derived compound **5y** a single fraction was obtained. Interestingly, the ^{1}H NMR spectra of **5y** presented four well-resolved and equally intense signals at 5.12, 5.20, 5.25 and 5.31 ppm, corresponding to the imidazolidinone NC*H*N resonance, suggesting that equal amounts of all four diastereomers were formed. In contrast, it was possible to isolate two pure diastereomers of **5x**, each one presenting a singlet at ca. 5.1 ppm, corresponding to the imidazolidinone NC*H*N resonance, and three singlets at 3.7–3.9 ppm, corresponding to each of the CH_3O resonances. In addition, a 1:1 mixture of the other two diastereomers of **5x** was also isolated, as indicated by the two equally intense singlets at ca. 5.0 ppm and six singlets in the 3.7–3.9 ppm region. The compounds derived from alanine, **5v**, and valine, **5w**, had an intermediate behaviour: two fractions could be isolated in both cases, each of which corresponded to different combinations of the four diastereomers.

The reactions of compounds **3a**–**e** with 2-formylbenzoic acid afforded the corresponding 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones, **6a**–**e** in good yields (44–60%). Mass spectrometric analysis of crude **6e** exhibited a signal at *m*/*z*=538.6 corresponding to the imidazolidin-4-one intermediate that is formed prior to the cyclization that leads to the formation of the isoindole ring. The structural assignment of compounds **6** is based on spectroscopic data. For the glycine derivative **6a**, two diastereomeric pairs of enantiomers were to be expected, and it was indeed possible to separately isolate two fractions from the reaction of **3a** and 2-formylbenzoic acid. A characteristic feature of the ^{1}H NMR spectrum of each enantiomeric pair of **6a** is the resonance of the NC*H*N group, which appears as a singlet at 5.6–5.8 ppm. Moreover, the glycine CH_2 signal appears as two doublets with typical geminal coupling constants (^2J=11.7 Hz), reflecting the diastereotopic nature of the methylene protons. In contrast, compounds **6b**–**e** were formed as mixtures of non-isolable diastereomers. However, the following ^{1}H and ^{13}C NMR data suggest the formation of only two diastereomers in each case, even though a total of four was anticipated. First, the resonance of the NC*H*N proton (H_{9b}) appears as two 1:1 singlets at 5.7–5.9 ppm. Second, the ^{13}C NMR spectra of **6b**–**e** presented duplication for, among others: the C-5 and C-7 quinoline carbons; the C-1′, C-2′, C-3′ and C-4′ amine side-chain carbons; and the C-2, C-3 and C-5 atoms of the 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione system.

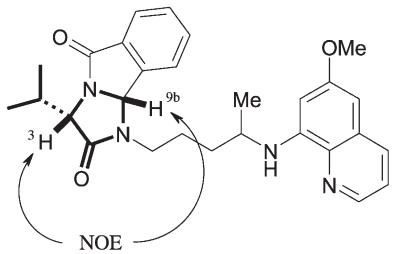


Figure 1. NOE effect of the *cis*-isomer of **6c** as observed in $CDCl_3$ at 300 K.

In order to determine the absolute configuration of the new chiral center in **6b**–**e** we carried out NOE experiments. For compound **6c**, irradiation of C_{9b}–H of each diastereomer led to a clear positive NOE-effect for the C_3–H (Fig. 1) and for one of the methyls in the isopropyl side chain. In contrast, no significant effect was observed for hydrogen $(CH_3)_2CH$ in the same group upon irradiation of C_{9b}–H. Similar results were obtained for **6b** and **6d**: irradiation of C_{9b}–H of each **6b** diastereomer caused a positive NOE for the C_3–H and had no effect on the hydrogen atoms of the CH_3; irradiation of the C_{9b} proton in compound **6d** caused positive NOEs on C_3–H and $(CH_3)_2CHCH_2$, but no effect

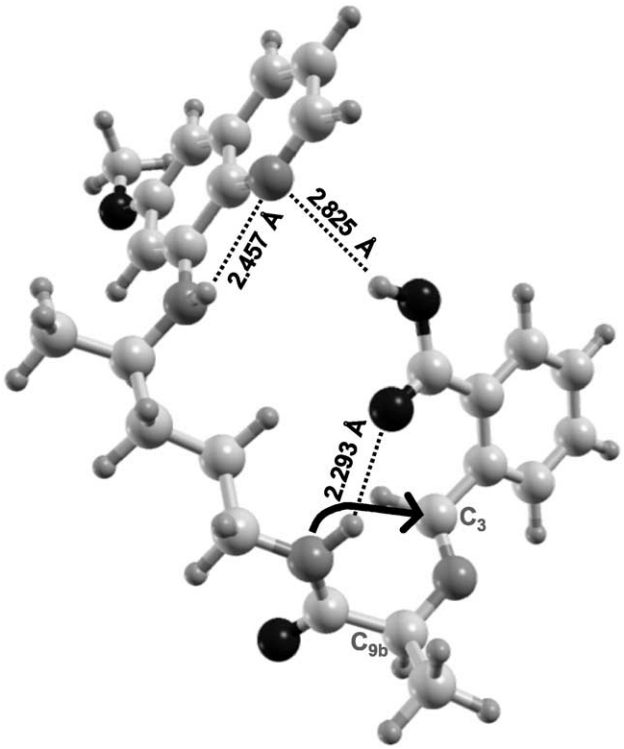


Figure 2. AM1-optimised structure of the imine intermediate formed from 2-formylbenzoic acid and the N-acylprimaquine **3b**. Small spheres=H; black spheres=O; dark grey spheres=N; light grey spheres=C; dotted lines show intramolecular hydrogen bonds and their lengths are also displayed; black arrow depicts the favoured orientation for ring closure leading to a final 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione structure with C_3-H and C_{9b}-H atoms in *cis*-orientation (see text).

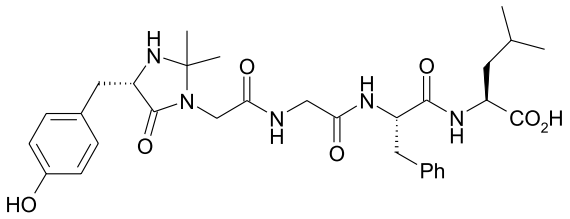
on $(CH_3)_2CHCH_2$. These findings suggest that the C_3-H and $C_{9b}-H$ have a *cis* orientation. This contrasts with results obtained by Katritzky and co-workers, who found that stereoselective syntheses of 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones led to the *trans*-orientation of C_3-H and $C_{9b}-H$.[28] The cause of such difference is not clear. The reaction path leading to 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones is essentially the same as for imidazolidin-4-ones, that is, imine formation followed by intramolecular cyclization to the imidazolidinone structure, including an additional step for the intramolecular amide bond formation that generates the final pyrrolidinone structure. A possible explanation is that the *o*-carboxyl substituent in 2-formylbenzoic acid could establish a hydrogen bond with the amide group, yielding a rigid conformation that would constrain the stereochemistry of the subsequent intramolecular cyclization step. The lack of any such constraint in veratraldehyde would explain its different behaviour. To evaluate the validity of this hypothesis, we have performed semi-empirical calculations at the AM1 level[29] to optimise the geometry of the imine intermediate formed upon reaction with 2-formylbenzoic acid. The simplest chiral amino acid, alanine, was considered, and the calculations yielded the optimised structure depicted in Figure 2. This structure clearly shows three intramolecular hydrogen bonds that stabilize the folding of the imine and favours a stereo-controlled cyclization. This leads to a final 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione structure where atoms C_3-H and $C_{9b}-H$ are *cis*-oriented, which is in agreement with the NOE experiments. A final confirmation of this rationale could be given by X-ray diffraction experiments. Unfortunately, compounds **6** are all oils and all attempts to obtain crystals have been unsuccessful.

2.3. In vitro assessment of imidazolidin-4-ones 5 as potential prodrugs

The reactivity of several imidazolidin-4-ones **5** derived from ketones in pH 7.4 phosphate buffer at 37 °C was assessed by HPLC. Quite surprisingly, compounds **5** hydrolyse very slowly, though quantitatively, to the corresponding amino acid derivative **3** (Table 1). This behaviour contrasts with the rapid hydrolysis of their counterparts **4** derived from a dipeptide framework. For example the 2,2-dimethylimidazolidin-4-one **5a**, derived from HGlyPQ, **3a**, is hydrolysed ca. 100 times slower than their counterparts **4** derived from Gly-Phe or Gly-Tyr.[16] The same trend is observed when comparing derivatives **5** with imidazolidin-4-ones derived from higher peptides. For example, compound **5e** derived from HPhePQ, **3e**, is hydrolysed 60 times slower than the Leu-enkephalin derivative **8**.[17] The rates of hydrolysis of **5** are largely affected by the substituents at C-2 of the imidazolidin-4-one moiety, with those derived from cyclopentanone, **5h** and **5j**, being significantly more reactive than those derived from acetone or cyclohexanone. Unfortunately, derivatives **5** derived from cycloheptanone displayed very low aqueous solubility precluding their study in the pH 7.4 phosphate buffer. The results presented herein indicate that imidazolidin-4-ones **5** will likewise hydrolyse slowly in vivo and thus can be considered as slow-release systems of the amino acid derivatives of primaquine.

Table 1. Rate of hydrolysis of imidazolidin-4-ones 5 in pH 7.4 phosphate buffer at 37 °C

Compound	$t_{1/2}$ (d)
5a	9.8
5c	12
5e	31
5h	8.8
5j	6.4
5l	12
5m	26



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3. Conclusion

In summary, amino acid derivatives, **3**, of primaquine can be converted to the corresponding imidazolidin-4-ones **5** in good yields by reaction with both cyclic and acyclic ketones and aromatic aldehydes. Cyclization of **3** with an unsymmetrical carbonyl (veratraldehyde) yields mixtures of all four possible stereomers. However, when cyclization was carried out with an *o*-carboxylated aldehyde, diastereoselectivity was encountered, since only two out of four possible stereomers of the corresponding 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6** were formed. The low rates of hydrolysis of imidazolidin-4-ones **5** in physiological conditions suggest that they may be useful as slow-release forms of the parent amino acid derivatives **3**.

4. Experimental

4.1. General details

N^{α}-Protected amino acids were purchased from NovaBiochem (Switzerland). Solvents were of p.a. quality and bought from Merck (Germany). Both thin layer chromatography (TLC) aluminium foil plates covered with silica 60 F_{254} (0.25 mm) and silica-gel 60 (70–230 mesh ASTM) for preparative column chromatography were also purchased from Merck. When required, solvents were previously dried with pre-activated molecular sieves (4 Å) (Merck). Other chemicals were obtained from Sigma-Aldrich.

NMR spectra of compounds dissolved in deuterated chloroform ($CDCl_3$), containing tetramethylsilane (TMS) as internal reference, were acquired on a Bruker AMX-300 spectrometer. Mass spectrometry (MS) was performed by the matrix-assisted laser desorption ionization—time-of-flight (MALDI-TOF) technique on an Applied Biosystems

Voyager STR-DE spectrometer, using either anthracene or 2,5-dihydroxibenzoic acid (DHB) as adjuvant matrices.

4.2. Condensation of PQ with N$^{\alpha}$-Boc protected amino acids—synthesis of compounds 7a–e

Compounds **7a–e** were prepared by condensation of PQ with N$^{\alpha}$-Boc-protected amino acids by the carbodiimide/1-hydroxybenzotriazole (DCCI or DIPCDI/HOBt) method. Briefly, primaquine bis[dihydrogenophosphate] (3.3 mmol) was suspended in dichloromethane (DCM, 30 mL), TEA (14 mmol) was added and the mixture was stirred in an ice-water–NaCl bath for 30 min. After addition of the BocAAOH (3.3 mmol) and HOBt (4.0 mmol), the carbodiimide (DCCI or DIPCDI, 4.0 mmol) was slowly added to the mixture, which was kept at 0 °C for 2 h more. The reaction was allowed to proceed at room temperature for 2 d, with periodic monitoring by TLC. A second stepwise addition of carbodiimide (4.0 mmol) was made, and the reaction prolonged for a further 3 d. The solid phase formed was removed by suction filtration and identified as the carbodiimide-derived urea (DCU or DIU). The filtrate was evaporated to dryness and the residue dissolved in the minimum amount of warm acetone; the resulting solution was stored overnight at 4 °C and the urea precipitated was again removed by suction filtration. The filtrate was evaporated to dryness and the residue submitted to column chromatography on silica-gel, using DCM/acetone mixtures as eluents (in the proportions of 5:1 for compounds **7a–c** and 10:1 for compounds **7d–e**). Products **7a–e** were isolated as yellow-orange oils in 78–93% yields and successfully characterized by high-resolution MS and NMR, as detailed below.

4.2.1. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-2-oxooctyl}carbamic acid *tert*-butyl ester (7a). δ_H ($CDCl_3$, 300 MHz) 8.50 (dd, 1H, J=4.20, 1.47 Hz); 7.90 (dd, 1H, J=8.22, 1.65 Hz); 7.28 (dd, 1H, J=8.22, 4.20 Hz); 6.31 (d, 1H, J=2.56 Hz); 6.24 (d, 1H, J=2.56 Hz); 6.17 (m, 1H); 5.97 (m, 1H); 5.16 (m, 1H); 3.87 (s, 3H); 3.72 (d, 2H, J=5.88 Hz); 3.61 (m, 1H); 3.28 (m, 2H); 1.57 (m, 4H); 1.40 (s, 9H); 1.27 (d, 3H, J=6.24 Hz). δ_C ($CDCl_3$, 300 MHz) 169.3; 159.4; 156.0; 144.9; 144.3; 135.3; 134.8; 129.9; 121.9; 96.8; 91.7; 80.2; 55.2; 50.8; 50.7; 47.8; 44.4; 39.3; 37.5; 34.4; 33.7; 30.9; 28.3; 26.2; 20.5. m/z ($MW_{monoisotopic}$)=416.2107 (Calcd, 416.24).

4.2.2. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-methyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7b). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.22, 1.64 Hz); 7.87 (dd, 1H, J=8.28, 1.60 Hz); 7.30 (dd, 1H, J=8.25, 4.23 Hz); 6.47 (m, 1H); 6.33 (d, 1H, J=2.48 Hz); 6.26 (d, 1H, J=2.48 Hz); 5.98 (d, 1H, J=8.25 Hz); 5.19 (m, 1H); 4.13 (m, 1H); 3.68 (s, 3H); 3.61 (m, 1H); 3.26 (m, 2H); 3.28 (m, 2H); 1.64 (m, 4H); 1.39 (s, 9H); 1.33 (d, 3H, J=6.46 Hz); 1.27 (d, 3H, J=6.24 Hz). δ_C ($CDCl_3$, 300 MHz) 172.6; 159.3; 155.5; 144.8; 144.2; 135.3; 134.8; 129.8; 121.8; 96.7; 91.6; 79.9; 55.1; 50.0; 48.9; 47.7; 39.2; 33.9; 33.6; 28.2; 26.1; 25.6; 24.9; 20.5; 18.5. m/z ($MW_{monoisotopic}$)=430.2658 (Calcd, 430.26).

4.2.3. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-isopropyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7c). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.05, 1.35 Hz); 7.90 (dd, 1H, J=8.25, 1.35 Hz); 7.28 (dd, 1H, J=7.25, 4.95 Hz); 6.53 (m, 1H); 6.33 (d, 1H, J=2.10 Hz); 6.27 (d, 1H, J=2.10 Hz), 5.99 (d, 1H, J=7.20 Hz); 5.30 (dd, 1H, J=8.25, 2.00 Hz); 3.92 (m, 1H); 3.87 (s, 3H); 3.59 (m, 1H); 3.25 (m, 2H); 2.05 (m, 1H); 1.63 (m, 4H); 1.39 (s, 9H); 1.27 (d, 3H, J=6.00 Hz); 0.93 (d, 3H, J=6.90 Hz); 0.90 (d, 3H, J=6.90 Hz). δ_C ($CDCl_3$, 300 MHz) 171.7; 159.4; 156.0; 144.9; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.7; 79.7; 60.0; 55.1; 50.8; 50.7; 47.8; 47.7; 44.4; 39.3; 39.2; 33.9; 33.8; 30.9; 28.3; 26.3; 26.2; 20.5; 19.3; 17.9. m/z ($MW_{monoisotopic}$)=458.1214 (Calcd, 458.29).

4.2.4. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-isobutyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7d). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, J=4.10, 1.70 Hz); 7.92 (dd, 1H, J=7.50, 1.70 Hz); 7.31 (dd, 1H, J=7.50, 4.10 Hz); 6.34 (d, 1H, J=2.00 Hz); 6.31 (m, 1H); 6.27 (d, 1H, J=2.00 Hz); 5.99 (d, 1H, J=8.20 Hz); 4.99 (m, 1H); 4.05 (m, 1H); 3.89 (s, 3H); 3.63 (m, 1H); 3.27 (m, 2H); 2.12 (m, 1H); 1.66 (m, 6H); 1.41 (s, 9H); 1.29 (d, 3H, J=6.00 Hz); 0.92 (d, 3H, J=6.90 Hz); 0.90 (d, 3H, J=6.90 Hz). δ_C ($CDCl_3$, 300 MHz) 172.5; 159.3; 156.0; 144.8; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.6; 80.2; 68.7; 55.2; 49.0; 47.8; 47.7; 33.9; 33.7; 33.6; 30.3; 28.2; 26.2; 26.1; 25.6; 24.9; 24.7; 22.9; 20.5. m/z ($MW_{monoisotopic}$)=472.3163 (Calcd, 472.30).

4.2.5. N-{7-[(6-Methoxyquinolin-8-yl)amino]-3-aza-1-benzyl-2-oxooctyl}carbamic acid *tert*-butyl ester (7e). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.17, 1.55 Hz); 7.91 (dd, 1H, J=8.31, 1.59 Hz); 7.32–7.12 (m, 6H); 6.33 (d, 1H, J=2.90 Hz); 6.25 (d, 1H, J=2.90 Hz); 6.03 (m, 1H); 5.58 (m, 1H); 4.27 (m, 1H); 3.87 (s, 3H); 3.52 (m, 1H); 3.17 (m, 2H); 3.15 (d, 2H, J=6.68 Hz); 1.49 (m, 4H); 1.37 (s, 9H); 1.25 (d, 3H, J=6.33 Hz). δ_C ($CDCl_3$, 300 MHz) 173.9; 173.8; 159.3; 156.0; 144.8; 144.1; 136.8; 136.7; 135.2; 134.6; 129.7; 129.5; 128.4; 126.7; 121.7; 96.5; 91.4; 75.9; 58.6; 55.0; 47.8; 47.6; 40.1; 40.0; 36.8; 36.7; 33.9; 33.8; 27.8; 26.2; 26.1; 25.9; 25.8; 20.5. m/z ($MW_{monoisotopic}$)=506.2019 (Calcd, 506.29).

4.3. Acidic removal of the N$^{\alpha}$-Boc protecting group—synthesis of compounds 3a–e

Compounds **7a–e** were dissolved in a small volume of neat trifluoroacetic acid (TFA, ca. 5 mL) and the deprotection reactions allowed to proceed for 1–2 h at room temperature. Excess TFA was neutralized by dropwise addition of aqueous Na_2CO_3 at 30% until pH 10; the supernatant oily phase formed in this process was extracted seven times with 10-mL portions of chloroform and the organic phases pooled, dried over anhydrous $MgSO_4$ and evaporated to dryness. Products **3a–e** were thus isolated as yellow-orange oils in 83–97% yields and successfully characterized by high-resolution MS and NMR, as detailed below.

4.3.1. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-aminoacetamide (3a). δ_H ($CDCl_3$, 300 MHz) 8.48 (dd, 1H, J=4.23, 1.65 Hz); 7.87 (dd, 1H, J=9.51, 1.29 Hz); 7.26 (dd, 1H, J=9.72, 4.23 Hz); 6.30 (d, 1H, J=2.56 Hz); 6.24

(d, 1H, *J*=2.56 Hz); 5.92 (m, 1H); 3.83 (s, 3H); 3.53 (m, 1H); 3.39 (m, 2H); 3.19 (m, 2H); 1.59 (m, 4H); 1.20 (d, 3H, *J*=6.21 Hz). δ_C ($CDCl_3$, 300 MHz) 159.4; 144.9; 144.3; 137.4; 135.3; 134.8; 129.9; 121.9; 96.9; 91.7; 78.1; 77.2; 55.2; 48.2; 47.9; 47.8; 43.7; 43.3; 40.2; 39.7; 39.5; 39.2; 39.1; 26.4; 26.3; 26.1; 20.6; 20.5. *m/z* ($MW_{monoisotopic}$)=316.1992 (Calcd, 316.19).

4.3.2. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-aminopropanamide (3b). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.20, 1.53 Hz); 7.92 (dd, 1H, *J*=8.25, 1.51 Hz); 7.31 (dd, 1H, *J*=8.22, 4.20 Hz); 6.34 (d, 1H, *J*=2.45 Hz); 6.28 (d, 1H, *J*=2.45 Hz); 6.00 (d, 1H, *J*=8.29 Hz); 3.89 (s, 3H); 3.63 (m, 1H); 3.46 (m, 1H); 3.27 (m, 2H); 1.80 (m, 2H); 1.63 (m, 4H); 1.31 (d, 3H, *J*=6.19 Hz); 1.29 (d, 3H, *J*=6.72 Hz). δ_C ($CDCl_3$, 300 MHz) 159.4; 144.9; 144.2; 135.3; 134.8; 129.9; 121.9; 96.8; 91.6; 55.2; 50.7; 47.8; 38.9; 33.8; 26.3; 21.7; 20.5. *m/z* ($MW_{monoisotopic}$)=330.1082 (Calcd, 330.21).

4.3.3. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-amino-3-methylbutanamide (3c). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=3.60, 0.90 Hz); 7.90 (dd, 1H, *J*=8.10, 1.20 Hz); 7.28 (dd, 1H, *J*=7.50, 5.10 Hz); 6.32 (d, 1H, *J*=1.95 Hz); 6.28 (d, 1H, *J*=1.95 Hz), 6.01 (d, 1H, *J*=8.10 Hz); 3.87 (s, 3H); 3.62 (m, 1H); 3.28 (m, 2H); 3.16 (m, 1H); 2.25 (m, 1H); 1.65 (m, 4H); 1.53 (s, 2H); 1.29 (d, 3H, *J*=6.60 Hz); 0.95 (d, 3H, *J*=7.20 Hz); 0.78 (dd, 3H, *J*=6.90, 2.40 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 159.4; 144.9; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.7; 77.3; 63.9; 60.1; 55.2; 47.8; 47.7; 38.9; 38.8; 33.9; 33.8; 30.8; 26.4; 26.3; 20.5; 19.7; 16.0. *m/z* ($MW_{monoisotopic}$)=358.1878 (Calcd, 358.24).

4.3.4. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-amino-4-methylpentanamide (3d). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.90, 1.60 Hz); 7.91 (dd, 1H, *J*=6.80, 1.60 Hz); 7.38 (m, 1H); 7.30 (dd, 1H, *J*=8.20, 4.90 Hz); 6.33 (d, 1H, *J*=2.60 Hz); 6.28 (d, 1H, *J*=2.60 Hz); 6.00 (d, 1H, *J*=8.20 Hz); 3.88 (s, 3H); 3.62 (m, 1H); 3.35 (m, 2H); 3.28 (m, 1H); 1.86 (m, 5H); 1.66 (m, 4H); 1.29 (d, 3H, *J*=6.33 Hz); 0.93 (d, 3H, *J*=6.09 Hz); 0.90 (d, 3H, *J*=5.79 Hz). δ_C ($CDCl_3$, 300 MHz) 172.5; 159.3; 156.0; 144.8; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 91.6; 80.2; 68.7; 55.2; 49.0; 47.8; 47.7; 33.9; 33.7; 33.6; 30.3; 28.2; 26.2; 26.1; 25.6; 24.9; 24.7; 22.9; 20.5. *m/z* ($MW_{monoisotopic}$)=372.3335 (Calcd, 372.25).

4.3.5. N-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-amino-3-phenylacetamide (3e). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.22, 1.56 Hz); 7.93 (dd, 1H, *J*=8.36, 1.42 Hz); 7.34–7.16 (m, 6H); 6.33 (d, 1H, *J*=2.51 Hz); 6.27 (d, 1H, *J*=2.51 Hz); 3.88 (s, 3H); 3.57 (m, 2H); 3.28 (m, 2H); 3.21 (m, 1H); 2.66 (dd, 1H, *J*=13.7, 9.31 Hz); 1.62 (m, 6H); 1.30 (d, 3H, *J*=6.35 Hz). δ_C ($CDCl_3$, 300 MHz) 174.0; 159.3; 156.0; 144.8; 144.2; 137.8; 135.2; 134.6; 129.8; 129.2; 128.5; 126.7; 121.8; 96.6; 91.5; 56.3; 55.1; 47.7; 40.9; 38.9; 36.8; 33.7; 26.1; 20.4. *m/z* ($MW_{monoisotopic}$)=406.2477 (Calcd, 406.24).

4.4. Reaction of 3a–e with symmetrical ketones: synthesis of imidazolidin-4-ones 5a–t

Compounds **3a–e** (2 mmol) were mixed with an excess (4 mmol) of the appropriate ketone (acetone, cyclopentanone, cyclohexanone or cycloheptanone) and TEA (2 mmol) in dry methanol (10 mL) and the mixture refluxed for 3 d in the presence of 4 Å molecular sieves (1 g). The reaction was monitored by TLC and ketone was re-added (2 mmol) once per day. The molecular sieves were removed by decantation and the solution evaporated to dryness. The oily residue was submitted to column chromatography on silica-gel, eluted with DCM/THF (varying solvent proportions) or, for compound **5a**, DCM/ethanol 15:1 (v/v). Fractions containing the chromatographically homogeneous product were pooled and evaporated to dryness, yielding **5a–t** as yellow-orange oils (44–81%) that were analyzed by high-resolution MS and NMR, as detailed below.

4.4.1. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2,2-dimethylimidazolidin-4-one (5a). δ_H ($CDCl_3$, 300 MHz) 8.50 (dd, 1H, *J*=4.20, 1.80 Hz); 7.89 (dd, 1H, *J*=8.40, 1.80 Hz); 7.27 (dd, 1H, *J*=8.40, 4.20 Hz); 6.31 (d, 1H, *J*=2.40 Hz); 6.26 (d, 1H, *J*=3.00 Hz); 5.99 (d, 1H, *J*=7.80 Hz); 3.86 (s, 3H); 3.62 (m, 1H); 3.40 (s, 2H); 3.16 (m, 2H); 2.05 (m, 1H); 1.69 (m, 4H); 1.27 (m, 9H). δ_C ($CDCl_3$, 300 MHz) 173.6; 159.3; 144.9; 144.2; 135.2; 134.7; 129.8; 121.8; 96.7; 91.6; 78.1; 55.1; 48.1; 47.8; 40.1; 33.9; 26.3; 26.2; 26.1; 20.5. *m/z* ($MW_{monoisotopic}$)=356.1004 (Calcd, 356.22).

4.4.2. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2,2,5-trimethylimidazolidin-4-one (5b). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.23, 1.66 Hz); 7.92 (dd, 1H, *J*=8.28, 1.66 Hz); 7.30 (dd, 1H, *J*=8.28, 4.23 Hz); 6.33 (d, 1H, *J*=2.50 Hz); 6.28 (d, 1H, *J*=2.50 Hz); 6.00 (d, 1H, *J*=7.16 Hz); 3.88 (s, 3H); 3.64 (m, 1H); 3.50 (q, 1H, *J*=6.87 Hz); 3.32 (m, 1H); 3.04 (m, 1H); 1.93 (m, 1H); 1.72 (m, 4H); 1.32 (m, 12H). δ_C ($CDCl_3$, 300 MHz) 175.6; 159.3; 144.9; 144.2; 135.3; 134.7; 129.8; 121.8; 96.7; 91.6; 75.7; 55.2; 53.6; 47.8; 45.0; 40.3; 33.8; 28.1; 26.2; 25.8; 25.6; 20.5; 17.4. *m/z* ($MW_{monoisotopic}$)=370.2809 (Calcd, 370.24).

4.4.3. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-5-isopropyl-2,2-dimethylimidazolidin-4-one (5c). δ_H ($CDCl_3$, 300 MHz) 8.51 (d, 1H, *J*=3.60 Hz); 7.90 (d, 1H, *J*=7.80 Hz); 7.29 (dd, 1H, *J*=7.80, 3.60 Hz); 6.31 (d, 1H, *J*=2.10 Hz); 6.29 (d, 1H, *J*=2.10 Hz), 6.01 (m, 1H); 3.87 (s, 3H); 3.63 (m, 1H); 3.46 (m, 3H); 2.96 (m, 1H); 2.18 (m, 1H); 1.71 (m, 4H); 1.29 (m, 9H); 1.03 (d, 3H, *J*=6.90 Hz); 0.91 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.2; 166.0; 159.4; 145.5; 145.0; 144.3; 135.4; 134.7; 129.9; 121.8; 96.8; 91.7; 75.7; 65.8; 62.8; 55.2; 48.0; 47.7; 40.2; 40.0; 34.1; 34.0; 30.3; 28.9; 28.3; 26.6; 26.5; 26.2; 26.1; 20.6; 19.3; 16.7; 15.3. *m/z* ($MW_{monoisotopic}$)=398.2293 (Calcd, 398.27).

4.4.4. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-5-isobutyl-2,2-dimethylimidazolidin-4-one (5d). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 2.10 Hz); 7.90 (dd, 1H, *J*=8.40, 2.10 Hz); 7.38 (m, 1H); 7.28 (dd, 1H, *J*=8.40, 4.20 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 6.29 (d, 1H, *J*=2.40 Hz); 6.10 (d, 1H, *J*=6.60 Hz); 3.88 (s, 3H); 3.63 (m, 1H); 3.44 (dd, 1H, *J*=9.90, 3.30 Hz); 3.33 (m, 1H); 3.02 (m, 1H); 1.84 (m, 3H); 1.71 (m, 4H); 1.34 (d, 3H, 6.90 Hz), 1.30 (d, 3H, *J*=6.30 Hz); 0.96 (d, 3H, *J*=6.00 Hz); 0.94 (d, 3H,

J=6.00 Hz). δ_C ($CDCl_3$, 300 MHz) 175.7; 165.9; 159.4; 145.0; 144.3; 135.3; 134.7; 129.9; 121.8; 96.7; 91.6; 76.1; 56.3; 55.2; 47.9; 47.8; 41.7; 40.3; 40.2; 33.9; 28.2; 26.2; 26.1; 25.9; 25.3; 23.4; 21.5; 20.6; 20.5. m/z ($MW_{monoisotopic}$)=412.1843 (Calcd, 412.28).

4.4.5. 3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-5-benzyl-2,2-dimethylimidazolidin-4-one (5e). δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.90 (d, 1H, J=8.18 Hz); 7.22 (m, 6H); 6.32 (d, 1H, J=2.46 Hz); 6.28 (d, 1H, J=2.46 Hz); 6.00 (dd, 1H, J=8.24, 5.66 Hz); 3.87 (s, 3H); 3.75 (t, 1H, J=5.39 Hz); 3.61 (m, 1H); 3.33 (m, 1H); 3.07 (d, 2H, J=5.24 Hz); 2.94 (m, 1H); 1.63 (m, 5H); 1.28 (dd, 3H, J=6.34, 2.12 Hz); 1.20 (d, 3H, J=2.45 Hz); 1.08 (s, 3H). δ_C ($CDCl_3$, 300 MHz) 174.0; 159.4; 156.0; 145.0; 144.3; 136.9; 135.3; 134.7; 129.9; 129.6; 128.5; 126.6; 121.6; 96.7; 91.6; 76.1; 58.8; 55.2; 53.9; 47.9; 47.8; 40.3; 36.9; 34.0; 30.7; 29.3; 28.0; 26.4; 26.3; 26.1; 26.0; 20.6. m/z ($MW_{monoisotopic}$)=446.3802 (Calcd, 446.27).

4.4.6. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,4-diazaspiro[4.4]nonan-2-one (5f). δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.91 (d, 1H, J=8.40 Hz); 7.29 (dd, 1H, J=7.80, 4.20 Hz); 6.33 (m, 1H); 6.28 (m, 1H); 6.01 (d, 1H, J=8.10 Hz); 3.89 (s, 3H); 3.66 (m, 1H); 3.36 (s, 2H); 3.13 (m, 2H); 1.89 (bs, 1H); 1.72 (m, 8H); 1.54 (m, 4H); 1.30 (d, 3H, J=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 159.4; 145.0; 144.3; 135.3; 134.8; 129.9; 121.9; 96.7; 91.6; 88.1; 77.3; 76.8; 55.2; 48.3; 47.8; 40.1; 35.5; 35.4; 33.8; 26.2; 23.0; 20.6; 20.7. m/z ($MW_{monoisotopic}$)=382.2637 (Calcd, 382.24).

4.4.7. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,4-diazaspiro[4.4]nonan-2-one (5g). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.35, 1.65 Hz); 7.92 (dd, 1H, J=8.40, 1.20 Hz); 7.30 (dd, 1H, J=8.10, 4.20 Hz); 6.33 (d, 1H, J=2.40 Hz); 6.28 (d, 1H, J=2.40 Hz); 6.01 (m, 1H); 3.88 (s, 3H); 3.66 (m, 1H); 3.44 (q, 1H, J=10.0 Hz); 3.32 (m, 1H); 2.93 (m, 1H); 1.69 (m, 12H); 1.33 (d, 3H, J=6.30 Hz); 1.30 (d, 3H, J=5.40 Hz). δ_C ($CDCl_3$, 300 MHz) 176.3; 159.4; 145.0; 144.9; 144.3; 135.3; 134.8; 129.9; 121.8; 96.8; 96.7; 91.6; 85.9; 77.2; 55.2; 53.9; 48.0; 47.7; 40.4; 40.2; 37.5; 33.8; 30.3; 26.2; 23.2; 23.0; 20.7; 20.6; 17.0. m/z ($MW_{monoisotopic}$)=396.3026 (Calcd, 396.25).

4.4.8. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,4-diazaspiro[4.4]nonan-2-one (5h). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.35, 1.35 Hz); 7.91 (dd, 1H, J=8.25, 1.35 Hz); 7.28 (dd, 1H, J=7.95, 4.35 Hz); 6.32 (d, 1H, J=2.70 Hz); 6.29 (d, 1H, J=2.85 Hz), 6.02 (d, 1H, J=8.70 Hz); 3.88 (s, 3H); 3.64 (m, 1H); 3.37 (m, 1H); 3.32 (d, 1H, J=4.2 Hz); 2.87 (m, 1H); 2.15 (m, 1H); 1.80–1.50 (m, 12H); 1.30 (d, 3H, J=6.90 Hz); 1.02 (d, 3H, J=6.75 Hz); 0.90 (d, 3H, J=6.75 Hz). δ_C ($CDCl_3$, 300 MHz) 174.9; 174.8; 159.5; 159.4; 145.0; 144.3; 144.2; 135.4; 134.7; 129.9; 121.8; 96.8; 96.7; 91.6; 85.7; 77.3; 63.0; 55.2; 48.0; 47.6; 40.2; 39.9; 37.7; 35.5; 35.4; 34.1; 33.9; 28.9; 26.2; 26.0; 25.6; 23.1; 22.9; 20.7; 20.6; 19.3; 19.2; 17.1; 17.0. m/z ($MW_{monoisotopic}$)=424.1883 (Calcd, 424.28).

4.4.9. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,4-diazaspiro[4.4]nonan-2-one (5i). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.20, 1.50 Hz); 7.92 (dd, 1H, J=8.40, 1.50 Hz); 7.29 (dd, 1H, J=8.40, 4.20 Hz); 6.32 (d, 1H, J=2.40 Hz); 6.28 (m, 1H); 6.02 (m, 1H); 3.88 (s, 3H); 3.64 (m, 1H); 3.37 (dd, 1H, J=9.90, 3.90 Hz); 3.32 (m, 1H); 2.93 (m, 1H); 2.00–1.50 (m, 16H); 1.30 (d, 3H, J=6.30 Hz), 0.94 (m, 6H). δ_C ($CDCl_3$, 300 MHz) 176.4; 159.6; 145.1; 144.4; 135.4; 134.9; 130.0; 121.9; 96.9; 93.8; 91.8; 86.2; 56.6; 55.3; 48.1; 47.9; 41.4; 40.4; 40.3; 37.7; 35.2; 35.0; 34.1; 34.0; 26.3; 26.2; 25.3; 23.5; 23.4; 23.3; 21.9; 20.8; 20.7. m/z ($MW_{monoisotopic}$)=438.3199 (Calcd, 438.30).

4.4.10. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,4-diazaspiro[4.4]nonan-2-one (5j). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.36, 2.85 Hz); 7.92 (dd, 1H, J=8.26, 1.62 Hz); 7.32–7.17 (m, 6H); 6.33 (d, 1H, J=2.39 Hz); 6.28 (d, 1H, J=2.88 Hz); 6.00 (t, 1H, J=8.24 Hz); 3.88 (s, 3H); 3.68 (t, 1H, J=5.28 Hz); 3.61 (m, 1H); 3.36 (m, 1H); 3.12 (dd, 1H, J=14.3, 5.64 Hz); 3.07 (dd, 1H, J=14.3, 4.84 Hz); 2.86 (m, 1H); 1.79–1.48 (m, 12H); 1.29 (dd, 3H, J=6.35, 2.39 Hz). δ_C ($CDCl_3$, 300 MHz) 174.6; 174.5; 159.4; 159.3; 144.9; 144.2; 144.1; 136.8; 136.7; 135.3; 135.2; 134.7; 129.8; 129.6; 128.5; 126.8; 121.8; 96.6; 96.5; 91.5; 85.9; 77.2; 58.9; 58.8; 55.1; 47.9; 47.6; 40.2; 40.1; 37.3; 36.4; 36.3; 35.1; 34.9; 33.9; 33.8; 30.9; 26.1; 25.9; 20.6.; 20.5 m/z ($MW_{monoisotopic}$)=472.3531 (Calcd, 472.28).

4.4.11. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,4-diazaspiro[4.5]decan-2-one (5k). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.20, 1.50 Hz); 7.92 (dd, 1H, J=8.10, 2.70 Hz); 7.30 (dd, 1H, J=8.10, 4.20 Hz); 6.33 (d, 1H, J=2.70 Hz); 6.29 (d, 1H, J=2.70 Hz); 6.01 (d, 1H, J=8.40 Hz); 3.89 (s, 3H); 3.64 (m, 1H); 3.37 (s, 2H); 3.14 (m, 2H); 1.80 (bs, 1H); 1.74–1.48 (m, 14H); 1.30 (d, 3H, J=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 173.9; 159.4; 145.0; 144.2; 135.3; 134.7; 129.9; 121.8; 96.6; 91.5; 80.1; 77.2; 55.2; 48.0; 47.8; 39.8; 34.9; 34.8; 33.8; 30.3; 26.4; 25.6; 24.7; 22.5; 20.7. m/z ($MW_{monoisotopic}$)=396.0727 (Calcd, 396.25).

4.4.12. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,4-diazaspiro[4.5]decan-2-one (5l). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.31, 1.68 Hz); 7.92 (dd, 1H, J=8.24, 1.61 Hz); 7.30 (dd, 1H, J=8.28, 4.26 Hz); 6.33 (d, 1H, J=2.51 Hz); 6.28 (d, 1H, J=2.51 Hz); 6.01 (d, 1H, J=8.22 Hz); 3.88 (s, 3H); 3.63 (m, 1H); 3.44 (q, J=7.05 Hz+q, J=6.84 Hz, 1H); 3.32 (m, 1H); 2.96 (m, 1H); 1.76–1.40 (m, 14H); 1.32 (d, 3H, J=4.70 Hz); 1.30 (d, 3H, J=4.23 Hz). δ_C ($CDCl_3$, 300 MHz) 175.9; 159.3; 145.0; 144.9; 144.2; 135.3; 134.7; 129.8; 121.8; 96.7; 96.6; 91.5; 78.0; 77.4; 55.1; 53.4; 47.9; 47.6; 40.0; 39.8; 37.8; 37.7; 33.7; 33.6; 33.3; 33.2; 30.2; 26.4; 24.8; 22.9; 22.2; 20.7; 17.7; 15.2. m/z ($MW_{monoisotopic}$)=410.3247 (Calcd, 410.27).

4.4.13. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,4-diazaspiro[4.5]decan-2-one (5m). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, J=4.14, 1.50 Hz); 7.92 (dd, 1H, J=8.24, 1.59 Hz); 7.30 (dd, 1H, J=8.21, 4.20 Hz); 6.33 (d, 1H, J=2.50 Hz); 6.28 (d, 1H, J=2.50 Hz), 6.01 (d, 1H, J=8.38 Hz); 3.89 (s, 3H); 3.63 (m, 1H); 3.36 (d, 1H, J=3.99 Hz); 3.32 (m, 1H); 3.00 (m, 1H); 2.10 (m, 1H); 1.75–1.37 (m, 15H); 1.30 (d, 3H, J=6.36 Hz); 1.01 (d, 3H, J=6.94 Hz); 0.88 (d, 3H, J=6.80 Hz). δ_C ($CDCl_3$,

300 MHz) 174.3; 159.4; 145.0; 144.2; 135.3; 129.9; 121.8; 96.7; 91.5; 77.2; 62.5; 55.2; 48.0; 47.6; 39.8; 39.6; 37.6; 34.5; 34.0; 33.9; 29.3; 26.5; 24.8; 23.1; 22.9; 22.2; 20.7; 20.6; 19.2; 17.0; 16.9. *m/z* ($MW_{monoisotopic}$)=438.4114 (Calcd, 438.30).

4.4.14. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,4-diazaspiro[4.5]decan-2-one (5n). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 1.50 Hz); 7.92 (dd, 1H, *J*=8.40, 1.50 Hz); 7.30 (dd, 1H, *J*=8.40, 4.20 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 6.29 (d, 1H, *J*=1.80 Hz); 6.02 (m, 1H); 3.88 (s, 3H); 3.64 (m, 1H); 3.38 (m, 1H); 3.30 (m, 1H); 2.98 (m, 1H); 1.98–1.29 (m, 18H); 1.30 (d, 3H, *J*=6.30 Hz), 0.94 (m, 6H). δ_C ($CDCl_3$, 300 MHz) 176.0; 159.4; 145.0; 144.2; 135.3; 134.8; 129.9; 121.8; 96.8; 96.7; 91.6; 78.2; 56.1; 55.2; 48.0; 47.7; 42.0; 41.9; 40.0; 39.8; 37.8; 37.7; 33.9; 33.8; 33.7; 26.5; 25.4; 25.3; 24.8; 23.2; 22.9; 22.2; 21.8; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=452.3154 (Calcd, 452.32).

4.4.15. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,4-diazaspiro[4.5]decan-2-one (5o). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 1.83 Hz); 7.92 (dd, 1H, *J*=8.22, 1.47 Hz); 7.32–7.15 (m, 6H); 6.33 (m, 1H); 6.28 (m, 1H); 6.00 (m, 1H); 3.88 (s, 3H); 3.71 (m, 1H); 3.60 (m, 1H); 3.31 (m, 1H); 3.05 (dd, 2H, *J*=5.3, 2.75 Hz); 1.75–1.40 (m, 14H); 1.29 (dd, 3H, *J*=6.39, 1.83 Hz). δ_C ($CDCl_3$, 300 MHz) 175.4; 173.9; 159.2; 144.8; 144.7; 144.0; 137.1; 137.0; 135.0; 134.9; 134.5; 129.6; 129.5; 128.2; 126.5; 121.7; 96.4; 96.3; 91.4; 72.5; 58.5; 58.4; 55.0; 47.7; 47.6; 40.2; 40.1; 37.4; 37.3; 37.2; 37.1; 34.4; 34.2; 33.7; 33.6; 26.1; 24.4; 22.5; 22.0; 21.9; 20.5; 20.4 *m/z* ($MW_{monoisotopic}$)=486.7263 (Calcd, 486.30).

4.4.16. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,4-diazaspiro[4.6]undecan-2-one (5p). δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.91 (d, 1H, *J*=8.40 Hz); 7.29 (dd, 1H, *J*=7.80, 4.20 Hz); 6.33 (m, 1H); 6.28 (m, 1H); 6.01 (d, 1H, *J*=8.10 Hz); 3.89 (s, 3H); 3.66 (m, 1H); 3.36 (s, 2H); 3.13 (m, 2H); 1.89 (bs, 1H); 1.72–1.40 (m, 14H); 1.30 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 159.4; 145.0; 144.3; 135.3; 134.8; 129.9; 121.9; 102.2; 96.7; 91.6; 88.1; 77.3; 76.8; 55.2; 48.3; 47.8; 40.1; 35.5; 35.4; 33.8; 26.2; 23.0; 20.6; 20.7. *m/z* ($MW_{monoisotopic}$)=410.3558 (Calcd, 410.27).

4.4.17. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,4-diazaspiro[4.6]undecan-2-one (5q). δ_H ($CDCl_3$, 300 MHz) 8.49 (m, 1H); 7.89 (m, 1H); 7.28 (m, 1H); 6.30 (m, 1H); 6.26 (m, 1H); 6.01 (m, 1H); 3.86 (s, 3H); 3.65 (m, 1H); 3.43–3.23 (m, 2H); 3.03 (m, 1H); 1.68 (m, 6H); 1.51 (m, 5H); 1.40–1.17 (m, 9H). δ_C ($CDCl_3$, 300 MHz) 175.5; 175.4; 159.3; 144.9; 144.8; 144.1; 135.2; 134.8; 129.8; 121.7; 96.7; 96.6; 91.6; 91.5; 81.2; 55.1; 53.1; 47.7; 47.6; 47.5; 40.9; 40.8; 40.3; 40.2; 36.9; 36.8; 33.7; 33.6; 29.6; 29.5; 29.1; 26.0; 22.4; 22.1; 22.0; 20.6; 20.5; 20.4; 17.2. *m/z* ($MW_{monoisotopic}$)=424.2835 (Calcd, 424.28).

4.4.18. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,4-diazaspiro[4.6]undecan-2-one (5r). δ_H ($CDCl_3$, 300 MHz) 8.51 (dd, 1H, *J*=3.90, 1.35 Hz); 7.91 (dd, 1H, *J*=8.25, 1.35 Hz); 7.29 (dd, 1H, *J*=8.25, 3.90 Hz); 6.32 (d, 1H, *J*=2.70 Hz); 6.29+6.28 (d+d, 1H, *J*=2.70 Hz), 6.01 (dd, 1H, *J*=7.95, 3.15 Hz); 3.88 (s, 3H); 3.64 (m, 1H); 3.41 (m, 1H); 3.32 (d, 1H, *J*=4.50 Hz); 3.01 (m, 1H); 2.12 (m, 1H); 1.89 (m, 1H); 1.71–1.34 (m, 16H); 1.30 (d, 3H, *J*=6.60 Hz); 1.01 (d, 3H, *J*=6.90 Hz); 0.89 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 300 MHz) 174.3; 174.2; 159.5; 159.4; 145.1; 145.0; 144.3; 144.2; 135.4; 134.7; 129.9; 121.8; 96.8; 96.7; 91.6; 80.9; 80.8; 77.3; 62.3; 55.2; 47.9; 47.5; 41.0; 40.9; 40.2; 40.1; 38.2; 38.1; 34.0; 30.3; 29.5; 29.4; 29.3; 29.2; 26.2; 26.1; 25.6; 22.5; 22.4; 22.1; 21.9; 20.7; 20.6; 19.3; 19.2; 17.1; 17.0. *m/z* ($MW_{monoisotopic}$)=452.3847 (Calcd, 452.32).

4.4.19. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,4-diazaspiro[4.6]undecan-2-one (5s). δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=4.20, 1.80 Hz); 7.91 (dd, 1H, *J*=8.40, 1.80 Hz); 7.29 (dd, 1H, *J*=8.40, 4.20 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 6.28 (m, 1H); 6.02 (m, 1H); 3.88 (s, 3H); 3.64 (m, 1H); 3.36 (m, 2H); 3.05 (m, 1H); 1.93–1.24 (m, 20H); 1.30 (d, 3H, *J*=6.60 Hz), 0.94 (m, 6H). δ_C ($CDCl_3$, 300 MHz) 175.6; 159.5; 145.0; 144.2; 144.1; 135.3; 135.2; 134.8; 134.7; 130.0; 129.9; 121.8; 96.8; 96.7; 918; 81.5; 55.9; 55.2; 47.8; 47.6; 41.7; 41.6; 41.0; 40.4; 40.3; 37.4; 37.2; 33.9; 33.8; 33.7; 29.6; 29.5; 29.3; 29.2; 26.1; 25.4; 25.3; 23.2; 22.5; 22.4; 22.2; 22.0; 21.8; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=466.3315 (Calcd, 466.33).

4.4.20. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,4-diazaspiro[4.6]undecan-2-one (5t). δ_H ($CDCl_3$, 300 MHz) 8.52 (dq, 1H, *J*=50, 1.80 Hz); 7.91 (dt, 1H, *J*=8.40, 1.80 Hz); 7.32–7.14 (m, 6H); 6.32 (m, 1H); 6.27 (m, 1H); 5.99 (t, 1H, *J*=8.70 Hz); 3.88 (s, 3H); 3.67 (t, 1H, *J*=5.40 Hz); 3.61 (m, 1H); 3.37 (m, 1H); 3.11 (m, 3H); 1.64–1.18 (m, 20H); 1.29 (dd, 3H, *J*=6.36, 3.38 Hz). δ_C ($CDCl_3$, 300 MHz) 173.9; 173.8; 159.4; 145.0; 144.9; 144.2; 144.1; 136.9; 136.8; 135.3; 134.7; 129.8; 129.7; 128.4; 126.8; 121.8; 96.6; 96.5; 91.5; 81.3; 77.2; 58.3; 58.2; 55.1; 47.8; 47.5; 40.6; 40.4; 40.3; 37.9; 37.7; 36.6; 36.5; 33.9; 33.8; 29.5; 29.2; 26.1; 25.8; 25.6; 22.3; 22.0; 20.7;20.6 *m/z* ($MW_{monoisotopic}$)=500.3246 (Calcd, 500.32).

4.5. Reaction of compounds 3a–e with veratraldehyde—synthesis of imidazolidin-4-ones 5u–x

Compounds **3a–e** (2 mmol) were mixed with a small excess (2.2 mmol) of veratraldehyde and TEA (2 mmol) in dry methanol (10 mL). The mixture was refluxed for 3 d in the presence of 4 Å molecular sieves (1 g) with periodic monitoring by TLC. One to four new TLC spots could be detected in the different reaction mixtures. The molecular sieves were removed by decantation and the solution evaporated to dryness. The oily residue was submitted to column chromatography on silica-gel, eluted with DCM/THF (varying solvent proportions). Chromatographically homogeneous fractions were pooled and evaporated to dryness, yielding different combinations of the four possible diastereomers for each one of the imidazolidin-4-ones **5u–x**. Global yields ranged from 57 to 95%. The different fractions of **5u–x** were analyzed by MALDI-TOF MS and NMR, and spectral data are detailed below. The product derived from glycine could not be isolated and further characterized by NMR, but the expected molecular weight

(464.24) could be detected in the reaction mixture by MALDI-TOF MS (*m/z* 464.2755).

4.5.1. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-methylimidazolidin-4-one (5u). *Fraction* 1. δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.20, 1.50 Hz); 7.93 (dd, 1H, *J*=8.40, 1.50 Hz); 7.32 (dd, 1H, *J*=8.40, 4.20 Hz); 6.80–6.65 (m, 3H); 6.34 (m, 1H); 6.25 (m, 1H); 5.95 (m, 1H); 5.39+5.00 (s+s, 1H); 3.88 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H); 3.61 (m, 3H); 2.67 (m, 1H); 1.68–1.60 (m, 5H); 1.38–1.27 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 175.7; 175.6; 159.2; 149.6; 149.5; 149.4; 144.7; 144.6; 144.1; 135.1; 134.6; 134.5; 131.3; 131.2; 129.7; 128.0; 121.7; 119.1; 119.0; 111.0; 110.9; 108.9; 108.8; 96.8; 96.6; 91.6; 91.5; 74.8; 74.7; 55.7; 55.6; 54.9; 54.3; 54.1; 47.4; 47.3; 40.0; 34.0; 33.4; 32.5; 23.4; 22.8; 21.0; 20.5; 20.2; 18.1; 17.8. *m/z* ($MW_{monoisotopic}$)=478.3069 (Calcd, 478.26).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.53 (m, 1H); 7.92 (dd, 1H, *J*=8.40, 1.50 Hz); 7.32 (m, 1H); 6.81–6.74 (m, 3H); 6.33 (d, 1H, *J*=2.40 Hz); 6.25 (d, 1H, *J*=2.70 Hz); 5.94 (m, 1H); 5.18+5.17 (m+ms, 1H); 3.88 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H); 3.59 (m, 3H); 2.70 (m, 1H); 1.66–1.58 (m, 5H); 1.32–1.23 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 175.6; 175.5; 168.1; 159.3; 159.0; 149.8; 149.7; 149.4; 144.8; 144.7; 144.1; 135.2; 134.6; 134.5; 130.8; 130.7; 129.7; 128.1; 121.7; 119.9; 119.8; 119.7; 111.0; 110.9; 109.4; 109.3; 96.7; 96.5; 91.5; 91.4; 75.1; 75.0; 55.7; 55.6; 55.0; 54.9; 47.5; 47.4; 40.3; 40.1; 34.1; 33.6; 33.2; 32.5; 23.5; 23.3; 21.0; 20.5; 20.3; 18.0; 17.9. *m/z* ($MW_{monoisotopic}$)=478.3083 (Calcd, 478.26).

4.5.2. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-isopropylimidazolidin-4-one (5v). *Fraction* 1. δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.92 (d, 1H, *J*=7.80 Hz); 7.30 (dd, 1H, *J*=7.80, 4.20 Hz); 6.82–6.71 (m, 3H); 6.32 (d, 1H, *J*=2.40 Hz); 6.24 (d, 1H, *J*=2.10 Hz); 5.96 (m, 1H); 5.34+5.24+5.12 (d, *J*=1.20 Hz+d, *J*=1.20 Hz+d, *J*=1.50 Hz; 1H); 3.84–3.49 (m, 11H); 2.67 (m, 1H); 2.18 (m, 1H); 2.02 (bs, 1H); 1.68–1.42 (m, 5H); 1.24 (d, 3H, *J*=2.10 Hz); 1.05–0.92 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 174.3; 174.2; 159.4; 159.3; 149.7; 149.5; 145.0; 144.9; 144.8; 144.2; 135.3; 134.8; 134.7; 132.4; 132.3; 129.9; 121.9; 121.8; 119.6; 119.5; 119.4; 111.2; 111.1; 111.0; 109.0; 108.9; 97.0; 96.9; 96.8; 91.7; 91.6; 91.5; 76.6; 76.6; 63.9; 63.8; 55.9; 55.8; 55.2; 47.8; 47.6; 47.5; 40.3; 40.2; 40.1; 40.0; 33.9; 33.8; 33.1; 31.2; 31.1; 25.6; 23.7; 23.5; 20.7; 20.5; 19.5; 16.7; 16.6. *m/z* ($MW_{monoisotopic}$)=506.2897 (Calcd, 506.29).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.20, 2.10 Hz); 7.92 (dd, 1H, *J*=8.40, 1.50 Hz); 7.30 (dd, 1H, *J*=8.40, 4.20 Hz); 6.86–6.70 (m, 3H); 6.33 (d, 1H, *J*=2.10 Hz); 6.24 (m, 1H); 5.96 (m, 1H); 5.34+5.31+5.24+5.13 (d, *J*=2.10 Hz+d, *J*=1.50 Hz+d, *J*=1.80 Hz+d, *J*=1.50 Hz; 1H); 3.88–3.74 (m, 10H); 3.71–3.49 (m, 3H); 2.66 (m, 1H); 2.25 (m, 1H); 1.96 (bs, 2H); 1.68–1.44 (m, 4H); 1.24 (m, 3H); 1.07–0.92 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 174.4; 174.3; 174.2; 174.1; 159.5; 159.4; 149.9; 149.8; 149.7; 149.6; 149.5; 145.1; 145.0; 144.9; 144.8; 144.3; 135.4; 134.8; 134.7; 132.4; 131.6; 131.5; 129.9; 130.0; 121.9; 121.8; 120.2; 120.1; 119.6; 119.5; 119.4; 111.3; 111.2; 111.1; 111.0; 109.8; 109.7; 109.0; 108.9; 97.0; 96.9; 96.8; 96.7; 91.8; 91.7; 91.6; 91.5; 76.6; 76.5; 74.8; 74.7; 68.0; 64.2; 64.1; 64.0; 63.8; 56.0; 55.9; 55.8; 55.7; 55.2; 47.8; 47.7; 47.6; 47.5; 40.2; 40.1; 40.0; 33.9; 33.8; 31.2; 30.3; 29.3; 29.2; 25.6; 25.5; 23.8; 23.7; 23.6; 23.3; 22.7; 20.7; 20.6; 20.5; 20.4; 19.5; 19.4; 16.8; 16.7; 16.6. *m/z* ($MW_{monoisotopic}$)=506.2887 (Calcd, 506.29).

4.5.3. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-isobutylimidazolidin-4-one (5w). δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=4.25, 1.40 Hz); 7.92 (dd, 1H, *J*=8.24, 1.41 Hz); 7.31 (dd, 1H, *J*=8.22, 4.23 Hz); 6.82–6.68 (m, 3H); 6.34 (m, 1H); 6.24 (m, 1H); 5.96 (m, 1H); 5.37+5.30+5.22+5.15 (d, *J*=1.12 Hz+d, *J*=1.01 Hz+d, *J*=0.98 Hz+d, *J*=1.00 Hz; 1H); 3.97–3.72 (m, 11H); 3.59 (m, 2H); 2.66 (m, 1H); 1.94 (m, 2H); 1.58–1.50 (m, 5H); 1.25 (m, 3H); 0.94 (m, 6H). δ_C ($CDCl_3$, 75 MHz) 175.8; 175.7; 175.6; 165.7; 165.5; 159.3; 149.8; 149.6; 149.5; 149.4; 144.9; 144.8; 144.7; 144.2; 135.2; 134.7; 131.6; 130.8; 129.8; 121.8; 119.9; 119.8; 119.4; 119.3; 111.1; 111.0; 110.3; 109.5; 109.4; 108.9; 108.8; 96.8; 96.6; 96.5; 91.6; 91.5; 91.4; 75.4; 75.3; 75.2; 75.1; 57.7; 57.2; 57.1; 55.8; 55.7; 55.1; 47.6; 47.5; 42.0; 41.6; 40.3; 40.2; 40.1; 39.9; 33.7; 33.6; 33.1; 33.0; 30.2; 25.5; 25.2; 25.1; 23.5; 23.4; 23.2; 23.1; 21.4; 20.6; 20.5; 20.4. *m/z* ($MW_{monoisotopic}$)=520.4108 (Calcd, 520.30).

4.5.4. 2-(3,4-Dimethoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-5-benzylimidazolidin-4-one (5x). *Fraction* 1. δ_H ($CDCl_3$, 300 MHz) 8.50 (m, 1H); 7.92 (dd, 1H, *J*=8.30, 0.90 Hz); 7.34–7.12 (m, 6H); 6.78–6.64 (m, 3H); 6.33 (d, 1H, *J*=2.80 Hz); 6.23 (d, 1H, *J*=2.80 Hz); 5.93 (m, 1H); 5.05+4.97 (m+m, 1H); 4.05 (m, 1H); 3.87+3.85 (s+s, 3H); 3.84+3.82 (s+s, 3H), 3.80+3.75 (s+s, 3H); 3.55 (m, 2H); 3.10 (m, 1H); 2.97 (m, 1H); 2.56 (m, 1H); 2.15 (bs, 1H); 1.58–1.43 (m, 4H); 1.22 (d, 3H, *J*=6.70 Hz). δ_C ($CDCl_3$, 75 MHz) 173.9; 173.8; 159.4; 149.7; 149.6; 145.0; 144.9; 144.3; 137.5; 137.4; 135.3; 134.8; 134.7; 131.7; 129.9; 129.8; 128.5; 128.4; 126.8; 126.7; 121.9; 119.5; 111.1; 111.0; 109.1; 109.0; 96.8; 96.6; 91.6; 91.5; 75.5; 75.4; 60.1; 56.0; 55.9; 55.8; 55.2; 47.7; 47.6; 40.2; 40.0; 38.5; 33.6; 33.4; 30.3; 23.4; 23.3; 20.6; 20.4. *m/z* ($MW_{monoisotopic}$)=554.6603 (Calcd, 554.29).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.52 (dd, 1H, *J*=3.90, 1.80 Hz); 7.91 (dd, 1H, *J*=8.40, 1.80 Hz); 7.32–7.16 (m, 6H); 6.68 (d, 1H, *J*=8.40 Hz); 6.42 (dd, 1H, *J*=8.40, 2.10 Hz); 6.32 (m, 2H); 6.24 (d, 1H, *J*=2.40 Hz); 5.94 (m, 1H); 5.06 (d, 1H, *J*=0.90 Hz); 3.87 (s, 3H); 3.81 (s, 3H); 3.80 (m, 1H); 3.63 (s, 3H); 3.58 (m, 1H); 3.42 (dt, 1H, *J*=14.1, 7.10 Hz); 3.26 (dd, 1H, *J*=14.1, 5.70 Hz); 3.10 (dd, 1H, *J*=13.9, 4.50 Hz); 2.71 (dt, 1H, *J*=13.8, 6.90 Hz); 1.86 (bs, 1H); 1.58–1.43 (m, 4H); 1.24 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 75 MHz) 174.4; 166.1; 149.9; 149.4; 144.9; 144.2; 136.9; 135.3; 134.8; 130.6; 129.9; 129.8; 126.9; 121.8; 120.2; 111.0; 109.2; 96.9; 91.6; 75.6; 60.2; 55.9; 55.8; 55.2; 47.6; 40.6; 36.6; 34.2; 33.4; 30.3; 23.5; 20.6; 20.4. *m/z* ($MW_{monoisotopic}$)=554.6391 (Calcd, 554.29).

Fraction 3. δ_H ($CDCl_3$, 300 MHz) 8.53 (dd, 1H, *J*=3.90,

1.50 Hz); 7.92 (dd, 1H, *J*=8.40, 1.20 Hz); 7.32–7.19 (m, 6H); 6.60 (d, 1H, *J*=8.40 Hz); 6.44 (dd, 1H, *J*=7.80, 1.80 Hz); 6.32 (m, 2H); 6.21 (d, 1H, *J*=2.40 Hz); 5.94 (m, 1H); 5.20 (d, 1H, *J*=1.50 Hz); 3.87 (s, 3H); 3.84 (m, 1H); 3.80 (s, 3H); 3.57 (s, 3H); 3.48 (m, 2H); 3.28 (dd, 1H, *J*=14.1, 5.40 Hz); 3.12 (dd, 1H, *J*=13.8, 4.50 Hz); 2.66 (m, 1H); 1.86 (bs, 1H); 1.64–1.43 (m, 4H); 1.22 (d, 3H, *J*=6.60 Hz). δ_C ($CDCl_3$, 75 MHz) 174.4; 166.1; 149.9; 149.4; 144.9; 144.2; 136.9; 135.3; 134.8; 130.6; 129.9; 129.8; 126.9; 121.8; 120.2; 111.0; 109.2; 96.9; 91.6; 75.6; 60.2; 55.9; 55.8; 55.2; 47.6; 40.6; 36.6; 34.2; 33.4; 30.3; 23.5; 20.6; 20.4. *m/z* ($MW_{monoisotopic}$)=554.7268 (Calcd, 554.29).

4.6. Reaction of compounds 3a–e with 2-formylbenzoic acid—synthesis of 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*, 9b*H*)-diones 6a–e

Compounds **3a–e** (2 mmol) were mixed with a small excess of 2-formylbenzoic acid (2.2 mmol) and TEA (2 mmol) in dry methanol (10 mL). The mixture was refluxed for 3 d in the presence of 4 Å molecular sieves (1 g) with periodic monitoring by TLC. In the syntheses of compounds **6b–d** only one new spot could be detected in the reaction mixtures, whereas two spots could be distinguished in the reaction mixtures for the syntheses of **6a** and **6e**. Molecular sieves were removed by decantation and the solution evaporated to dryness. The oily residue was submitted to column chromatography on silica-gel, eluted with DCM/THF (varying solvent proportions). Chromatographically homogeneous fractions were pooled, evaporated to dryness and analyzed by NMR and MALDI-TOF MS. Global yields ranged from 44 to 60% and compounds **6b–e** were found to be mixtures of two diastereomers (NMR), whereas it was possible to isolate each of the two diastereomers of **6a**. In the purification of compound **6e**, a second fraction of impure product was collected and analyzed by MALDI-TOF MS, showing the presence of an *m/z* peak (538.34) compatible with the imidazolidin-4-one structure (Calcd, 538.26).

4.6.1. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6a).

Fraction 1. δ_H ($CDCl_3$, 300 MHz) 8.50 (dd, 1H, *J*=4.20, 1.20 Hz); 7.92 (dd, 1H, *J*=8.40, 1.20 Hz); 7.83 (d, 1H, *J*=7.80 Hz); 7.50–7.24 (m, 4H); 6.36 (d, 1H, *J*=2.40 Hz); 6.32 (d, 1H, *J*=2.40 Hz); 5.95 (m, 1H); 5.69 (s, 1H); 4.42 (d, 1H, *J*=16.2 Hz); 3.88 (s, 4H), 3.74 (d, 1H, *J*=16.2 Hz), 3.60 (m, 1H); 3.40 (m, 1H); 1.92-1.65 (m, 4H); 1.27 (d, 3H, *J*=6.60 Hz). δ_C ($CDCl_3$, 75 MHz) 173.1; 170.5; 159.2; 144.6; 144.2; 142.0; 135.1; 134.7; 132.7; 130.4; 129.8; 124.9; 123.6; 121.7; 96.8; 91.7; 74.7; 55.1; 47.7; 47.2; 40.5; 34.0; 33.1; 24.0; 20.4. *m/z* ($MW_{monoisotopic}$)=430.2296 (Calcd, 430.20).

Fraction 2. δ_H ($CDCl_3$, 300 MHz) 8.49 (dd, 1H, *J*=4.50, 1.50 Hz); 7.90 (dd, 1H, *J*=8.10, 1.50 Hz); 7.80 (d, 1H, *J*=7.80 Hz); 7.50–7.24 (m, 4H); 6.34 (d, 1H, *J*=2.10 Hz); 6.27 (d, 1H, *J*=2.10 Hz); 6.01 (m, 1H); 5.80 (s, 1H); 4.44 (d, 1H, *J*=16.2 Hz); 3.86 (s, 4H), 3.78 (d, 1H, *J*=16.2 Hz), 3.64 (m, 1H); 3.28 (m, 1H); 1.90-1.60 (m, 4H); 1.26 (d, 3H, *J*=6.30 Hz). δ_C ($CDCl_3$, 75 MHz) 173.1; 170.4; 159.2; 144.6; 144.2; 141.9; 135.1; 134.6; 132.6; 130.3; 129.8; 124.9; 123.6; 121.8; 96.8; 91.8; 74.6; 55.0; 47.7; 47.1; 40.1; 34.0; 33.4; 23.9; 20.5. *m/z* ($MW_{monoisotopic}$)=430.2315 (Calcd, 430.20).

4.6.2. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-methyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6b).

δ_H ($CDCl_3$, 300 MHz) 8.50 (m, 1H); 7.88 (m, 1H); 7.78 (m, 1H); 7.48–7.24 (m, 4H); 6.32 (m, 2H); 6.04 (m, 1H); 5.76 (s, 0.7H); 5.59 (s, 0.3H); 4.52 (m, 1H); 3.85 (s, 3H), 3.65 (m, 2H), 3.30 (m, 1H); 1.79-1.60 (m, 4H); 1.50-1.42 (m, 3H); 1.27-1.24 (m, 3H). δ_C ($CDCl_3$, 75 MHz) 173.1; 173.0; 172.7; 172.6; 159.1; 159.0; 144.4; 143.9; 141.7; 141.6; 135.1; 134.9; 134.4; 132.3; 132.0; 130.5; 130.0; 129.5; 129.4; 124.5; 123.5; 123.4; 121.5; 96.7; 96.6; 91.5; 91.4; 72.7; 72.6; 54.1; 54.0; 46.9; 46.8; 40.1; 39.7; 38.2; 33.8; 33.0; 32.6; 23.6; 20.3; 20.1; 16.7; 16.6. *m/z* ($MW_{monoisotopic}$)=444.2428 (Calcd, 444.22).

4.6.3. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isopropyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6c).

δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.94 (m, 1H); 7.86 (m, 1H); 7.52–7.23 (m, 4H); 6.37 (m, 1H); 6.32 (m, 1H); 6.01 (m, 1H); 5.80+5.71 (s+s, 1H); 4.28 (m, 1H); 3.90 (s, 3H), 3.70 (m, 2H), 3.30 (m, 1H); 2.34 (m, 1H); 1.80-1.62 (m, 4H); 1.31 (m, 3H); 1.19 (m, 3H); 0.99 (m, 3H). δ_C ($CDCl_3$, 75 MHz) 173.1; 171.5; 171.4; 158.8; 144.1; 143.6; 142.1; 142.0; 134.6; 134.1; 132.0; 131.9; 131.7; 129.6; 129.3; 129.2; 124.0; 123.2; 123.1; 121.2; 96.3; 91.2; 91.1; 74.1; 73.9; 64.1; 54.4; 46.8; 46.3; 39.9; 39.4; 32.9; 32.8; 23.6; 23.2; 20.0; 19.9; 19.0; 17.0. *m/z* ($MW_{monoisotopic}$)=472.3159 (Calcd, 472.25).

4.6.4. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-isobutyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6d).

δ_H ($CDCl_3$, 300 MHz) 8.52 (m, 1H); 7.94 (m, 1H); 7.85 (m, 1H); 7.51–7.24 (m, 4H); 6.38-6.30 (m, 2H); 6.01 (t, 1H, *J*=8.70 Hz); 5.82+5.70 (s+s, 1H); 4.48 (dt, 1H, *J*=11.4, 3.30 Hz); 3.89 (s, 3H), 3.87 (m, 1H); 3.69 (m, 2H), 3.40 (m, 1H); 1.92 (m, 2H); 1.80–1.67 (m, 4H); 1.31+1.29 (d, *J*=1.80 Hz+d, *J*=1.80 Hz; 3H); 1.12 (d, *J*=6.60 Hz, 3H); 1.02+0.99 (d, *J*=1.80 Hz+d, *J*=1.80 Hz; 3H). δ_C ($CDCl_3$, 75 MHz) 173.4; 173.3; 173.2; 159.4; 159.3; 144.8; 144.7; 144.3; 144.2; 142.1; 142.0; 135.2; 134.7; 134.3; 132.6; 130.8; 130.4; 129.9; 129.8; 125.3; 124.9; 123.8; 123.7; 123.3; 121.9; 121.8; 96.9; 96.8; 91.8; 91.7; 73.3; 73.1; 58.0; 57.9; 55.1; 47.4; 47.1; 40.5; 40.0; 39.8; 39.1; 33.4; 33.2; 24.1; 23.9; 23.2; 23.1; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=486.2896 (Calcd, 486.26).

4.6.5. 1-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-3-benzyl-1,9b-dihydroimidazo[2,1-*a*]isoindole-2,5-dione (6e).

δ_H ($CDCl_3$, 300 MHz) 8.54+8.52 (dd, *J*=4.20, 1.20 Hz+dd, *J*=4.20, 1.50 Hz; 1H); 7.95 (dd, 1H, *J*=8.40, 1.90 Hz); 7.84 (m, 1H); 7.45 (m, 1H); 7.34-7.14 (m, 9H); 6.37+6.35 (d+d, 1H, *J*=2.40 Hz); 6.29+6.26 (d+d, 1H, *J*=2.40 Hz); 5.95 (m, 1H); 4.84+4.80 (s+s, 1H); 4.77 (t, 1H, *J*=4.50 Hz); 3.90 (s, 3H), 3.62-2.96 (m, 5H); 1.61-1.31 (m, 4H); 1.26 (m, 3H). δ_C ($CDCl_3$, 75 MHz) 173.6; 173.5; 172.0; 171.8; 159.5; 144.9; 144.8; 144.4; 144.3; 134.8; 132.7; 132.6; 130.4; 130.3; 130.2; 130.1; 127.2; 125.1; 125.0; 123.8; 123.7; 122.0; 121.9; 96.9; 96.8; 91.9; 91.8; 74.3; 74.1; 60.2; 60.1; 55.2; 47.7; 47.1; 40.7; 40.2; 37.4; 37.3; 33.6; 33.5; 23.9; 23.4; 20.7; 20.6. *m/z* ($MW_{monoisotopic}$)=520.3128 (Calcd, 520.258).

4.7. Kinetics of hydrolysis

The kinetics of hydrolysis of imidazolidin-4-ones were studied by HPLC using a Waters® assembly equipped with a model 600 controlled pump and a model 991 photodiode-array detector set at 265 nm. The separation was performed on a Purospher®, 250×4.0-mm i.d. 5 μm analytical column. The mobile phase consisted of a mixture of acetonitrile and sodium acetate buffer (pH 4.75; 0.05 M) containing 10^{-3} M triethylamine. Two gradients were developed: one for the imidazolidin-4-one derivatives of phenylalanine and the other for the derivatives of valine. A gradient method using 50–90% (v/v) acetonitrile over 20 min was used for compounds **5a**, **5e**, **5j** and **5l**, while a gradient using 60–90% (v/v) acetonitrile over 20 min was used for compounds **5c**, **5h** and **5m**. Usually, a 10 μL aliquot of a 10^{-2} M stock solution of substrate in acetonitrile was added to 10 mL of the appropriate thermostatted buffer solution. At regular intervals, samples of the reaction mixture were analysed by HPLC. All reactions followed first-order kinetics over four half-lives.

4.8. Computational details

The geometry of the imine intermediate has been optimised by the semi-empirical AM1 method as included in the GAMESS-US suite of programs.[29] Several different starting geometries were considered to ensure that a minimum on the PES was reached. Harmonic vibrational frequencies were calculated through construction and diagonalisation of the Hessian matrices at the obtained optimised molecular geometries. The absence of negative wavenumbers allowed us to characterize the equilibrium geometries as true minima.

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Synthesis of methylated resveratrol and analogues by Heck reactions in organic and aqueous solvents

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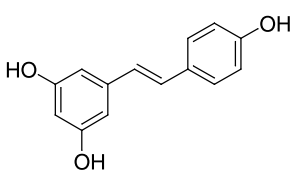
Dedicated to Professor José Luis Soto on occasion of his retirement

Abstract—The Heck reaction under phosphane free conditions using oxime-derived palladacycles or $Pd(OAc)_2$ as catalysts is a general methodology for the synthesis of methoxylated (*E*)-stilbene derivatives. Couplings can be performed either with (dicyclohexyl)methylamine as base and TBAB in aqueous DMA or in neat water and with Et_3N as base in DMA in air and under thermal and microwave conditions. The arylation of different styrenes are performed with 3,5-dimethoxyiodobenzene to afford a series of important biologically active (*E*)-stilbene derivatives containing the 3,5-dimethoxyphenyl moiety, including resveratrol, piceatannol and pinosilvine, which are efficiently prepared with high regioselectivity and total stereoselectivity (TON up to 10^4).

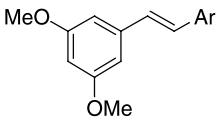
1. Introduction

Hydroxylated (*E*)-stilbenoids are natural polyphenols widely present in nature, especially in medicinal plants and food products,[1] which exhibit a variety of biological and therapeutical properties.[2–15] The phytoalexin resveratrol (**1**, Fig. 1), 3,4′,5-trihydroxy-(E)-stilbene, the biosynthetic precursor of most oligostilbenoids became the most famous compound as it was suggested as cancer chemopreventive agent[2] and due to its antiinflamatory[3] and antioxidative[4] properties may contribute also as chemoprotective agent.[5] In addition, it presents in vitro growth inhibition in a number of human cancer cell lines.[6] Resveratrol also prevents heart diseases due to lipid-lowering-activity and lipid peroxidation-inhibition.[7–9] Other properties, such as radical scavenging activity,[10] neuroprotection,[11] antiviral activity[12] and to promote survival and longevity by activating siruins[13] have also been recently found. For all these reasons new resveratrol analogues have been designed as chemotherapeutic agents.[14–16] For instance, the trimethyl ether of resveratrol **2a** shows more activity against several human cancer cell lines than resveratrol (**1**)[14] and methoxylated stilbenes, such as **2b** and **2c** are potent CYP1B1 inhibitors valuable for the development of a chemopreventive or therapeutic agent for cancer[16] (Fig. 1). Therefore, the development of general and simple strategies for the preparation of methoxylated stilbenoids for biological evaluation has became an important task.

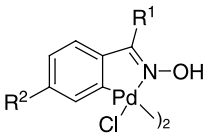
Several synthetic routes are based mainly on: (a) Wittig-type[1f,14–17] and modified Julia[18] olefinations, (b) reaction of 3,5-dimethoxybenzyllithium with 4-methoxybenzaldehyde followed by dehydration,[19] (c) Perkins reaction[20] (d) cross metathesis of styrenes,[21] (e) Suzuki reaction with β-halostyrenes,[22] (f) decarbonylative Heck reaction between resorcylic acid chloride and 4-acetoxystyrene,[23] (g)



1



2a: Ar = 4-$(MeO)C_6H_4$
2b: Ar = 2-thienyl
2c: Ar = 2,4-$(MeO)_2C_6H_3$



3a: R^1 = Me; R^2 = OH
3b: R^1 = 4-ClC_6H_4; R^2 = Cl

Figure 1.

Keywords: Resveratrol; Heck reaction; Palladacycles; Stilbenes; Styrenes.
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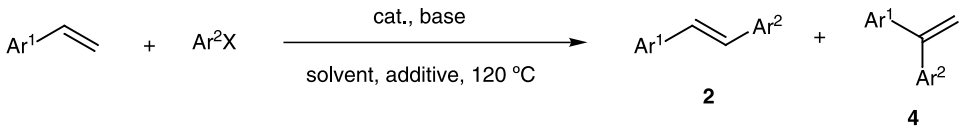


Scheme 1.

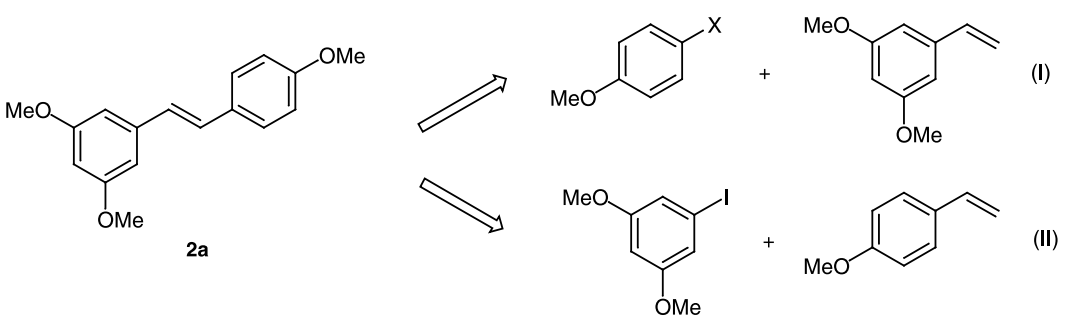
one-pot[24] sequential Heck arylation–desilylation of vinyltrimethylsilane followed by Heck arylation of styrene derivatives formed in situ and (h) by arylation of 3,5-dimethoxystyrene with 4-(benzyloxy)iodobenzene.[25] The main inconvenient for the palladium-catalyzed arylation of styrenes is the low reactivity of electron-rich styrenes and iodides.[26] Thus, the last two processes require the use of inert atmosphere and high loadings (2 mol%) of $Pd(dba)_2$[24] or the addition of silver nitrate at 120 °C during one week[25] to afford the corresponding resveratrol derivatives. As part of our project about the use of oxime-derived palladacycles **3** in C–C bond-forming reactions in organic[27] and aqueous media[28] we have focussed our attention on the possible applications of these catalysts for the synthesis of methoxylated stilbenes by Heck couplings of substituted aryl halides and styrenes.

2. Results and discussion

We first tested the arylation reaction of the rather reactive 4-chlorostyrene with activated 4-chlorophenyl and deactivated 4-methoxyphenyl iodides and bromides (Scheme 1 and Table 1) using 4-hydroxyacetophenone oxime-derived palladacycle **3a** as catalyst. However, under the reaction conditions established for arylation of acrylates,[28c] such as water reflux and (dicyclohexyl)methylamine as base the reaction was rather slow even with aryl iodides (Table 1, entries 1 and 4). When the process was performed in aqueous *N*,*N*-dimethylacetamide (DMA/H_2O: 4/1) at 120 °C (bath temperature) reaction times decreased, especially if 1 equiv of TBAB was added (Table 1, entries 2, 3 and 5, 6). For 4-chlorophenyl bromide the same effect was observed in aqueous DMA and TBAB as additive (Table 1, entries 7 and 8). Deactivated 4-methoxyphenyl bromide was coupled with 4-chlorostyrene under these conditions with palladacycle **3a** (0.5 mol% of Pd) in longer reaction times (1 d) and with $Pd(OAc)_2$[29] as catalyst only 2% conversion was observed (Table 1, entries 9 and 10). In all cases (*E*)-stilbene derivatives **2d** and **2e** with very low amounts of 1,1-diarylstyrenes **4** were observed and pure compounds **2** were isolated after flash chromatography.

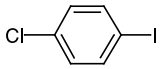
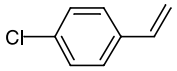
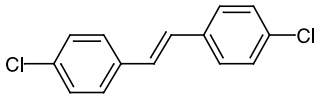
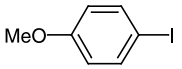
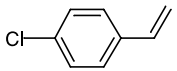
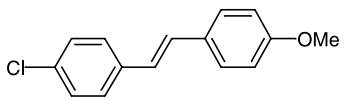
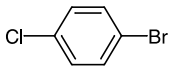
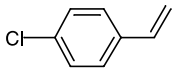
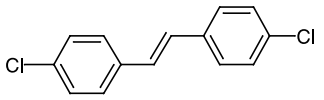
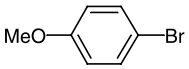
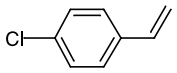
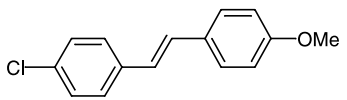
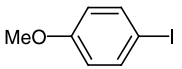
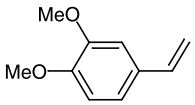
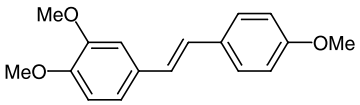
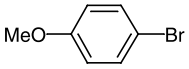
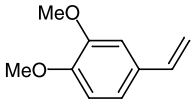
For subsequent studies between methoxylated partners commercially available 3,4-dimethoxystyrene and 4-methoxyiodobenzene were chosen as model substrates. For the couplings in aqueous DMA the presence of TBAB improved the efficiency of the catalyst **3a** (0.01 mol% Pd) (Table 1, entry 11) and Cy_2NMe as base gave better yields than Et_3N (Table 1, compare entries 11 and 12). On the other hand, under these reaction conditions, $Pd(OAc)_2$ led to the same results as complex **3a** (Table 1, compare entries 11 and 13). Couplings performed in neat DMA took place in shorter times in the presence of Et_3N instead of Cy_2NMe as base (Table 1, compare entries 14 and 15). In this case both palladacycles **3** and $Pd(OAc)_2$ were employed as catalysts, the former being the most active source of Pd (Table 1, entries 15–17). However, the coupling under water reflux and with Cy_2NMe as base failed. When 3,4-dimethoxystyrene was arylated with 4-methoxybromobenzene in DMA/H_2O, Cy_2NMe as base and TBAB as additive the amount of **3a** has to be increased to 0.5 mol% Pd to afford high conversions in 19 h. However, $Pd(OAc)_2$ failed as catalyst under these conditions (Table 1, compare entries 18 and 19). For couplings in DMA the presence of TBAB was necessary either with Cy_2NMe or Et_3N as base (Table 1, entries 20–22) and both catalysts **3a** and $Pd(OAc)_2$ gave similar results (Table 1, compare entries 21 and 23). Finally this coupling was carried out under Jeffery's conditions, so in the presence of K_2CO_3 as base the reaction was slower than with organic amines and $Pd(OAc)_2$ gave slightly better yields than palladacycle **3a** (Table 1, entries 24 and 25). From these studies we deduced that for the couplings of methoxylated styrene and aryl halides two method can be used, Method A: DMAc/H_2O, Cy_2NMe as base and TBAB as additive and either catalyst **3a** or $Pd(OAc)_2$ as catalysts except for aryl bromides, which required the use of **3a** and Method B: DMAc and Cy_2NMe or Et_3N as base, the presence of TBAB being required in the case of aryl bromides as arylating components. The regioselectivity was lower with 3,4-dimethoxystyrene than with 4-chlorostyrene and higher with aryl bromides than iodides.

For the preparation of biologically active 3,5-dimethoxy-(*E*)-stilbenes the use of different, commercially available or prepared by Wittig reaction,[30] aryl and heteroarylethylenes



Scheme 2.

Table 1. Reaction conditions optimization for the Heck reaction[a]

Entry	ArX	Styrene	Cat. (mol% Pd)	Amine	Solvent	Additive	t (h)	Product	
								No.	Yield (%)[b]
1			**3a** (1.1×10^{-2})	Cy_2NMe	H_2O	—	30	**2d** 	96 [16:1] (79)
2			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	—	20	**2d**	99 [15:1]
3			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	9	**2d**	99 [19:1]
4			**3a** (0.1)	Cy_2NMe	H_2O	—	72	**2e** 	89 [8.9:1] (75)
5			**3a** (0.1)	Cy_2NMe	DMA/H_2O	—	48	**2e**	86 [9.2:1]
6			**3a** (9.1×10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	9	**2e**	99 [12:1]
7			**3a** (0.52)	Cy_2NMe	DMA/H_2O	—	38	**2d** 	99 [24:1] (89)
8			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	15	**2d**	94 [25:1]
9			**3a** (0.5)	Cy_2NMe	DMA/H_2O	TBAB	24	**2e** 	87 [18:1] (81)
10			$Pd(OAc)_2$ (0.5)	Cy_2NMe	DMA/H_2O	TBAB	24	**2e**	2
11			**3a** (10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	19	**2f** 	99 [5.7:1]
12			**3a** (10^{-2})	Et_3N	DMA/H_2O	TBAB	20	**2f**	43 [7.3:1]
13			$Pd(OAc)_2$ (1.5×10^{-2})	Cy_2NMe	DMA/H_2O	TBAB	19	**2f**	98 [6.1:1]
14			**3a** (10^{-2})	Cy_2NMe	DMA	—	24	**2f**	99 [4.9:1]
15			**3a** (1.1×10^{-2})	Et_3N	DMA	—	3.5	**2f**	95 [4.6:1]
16			**3b** (9.1×10^{-3})	Et_3N	DMA	—	6	**2f**	91 [4.4:1]
17			$Pd(OAc)_2$ (10^{-2})	Et_3N	DMA	—	3.5	**2f**	86 [4.6:1]
18			**3a** (0.5)	Cy_2NMe	DMA/H_2O	TBAB	19	**2f**	84 [9.2:1]
19			$Pd(OAc)_2$ (0.5)	Cy_2NMe	DMA/H_2O	TBAB	19	**2f**	0
20			**3a** (0.5)	Cy_2NMe	DMA	—	24	**2f**	75 [7:1]
21			**3a** (0.5)	Cy_2NMe	DMA	TBAB	3.5	**2f**	99 [10:1]
22			**3a** (0.5)	Et_3N	DMA	TBAB	3.5	**2f**	80 [11.3:1]
23			$Pd(OAc)_2$ (0.5)	Cy_2NMe	DMA	TBAB	3.5	**2f**	99 [14.3:1]
24			**3a** (0.5)	K_2CO_3	DMA	TBAB	7.5	**2f**	82 [10.3:1]
25			$Pd(OAc)_2$ (0.5)	K_2CO_3	DMA	TBAB	7.5	**2f**	99 [9.9:1]

[a] Reaction conditions: ArX (1 mmol), styrene (1.5 mmol), amine (1.5 mmol), TBAB (1 mmol), H_2O (3 mL) or DMA/H_2O (4/1, 5 mL) or DMA (3 mL), 120 °C (bath temperature), pressure tube. For 10^{-2} mol% Pd: ArX (2 mmol), styrene (3 mmol), amine (3 mmol), TBAB (2 mmol).

[b] Conversion determined by GC based on ArX using decane as an internal standard. In brackets, regioisomers ratio of crude product (determined by GC). In parenthesis, isolated yield of the (*E*)-stilbene after flash chromatography (hexane/EtOAc).

Table 2. Synthesis of methoxylated (*E*)-stilbene derivatives

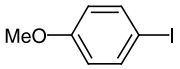
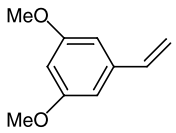
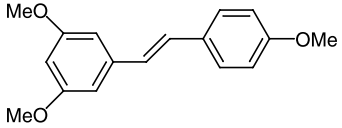
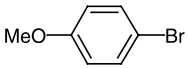
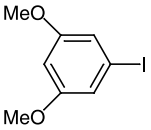
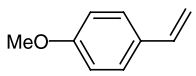
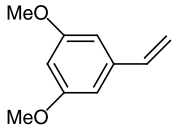
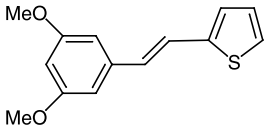
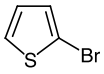
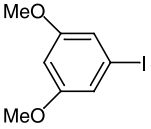
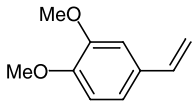
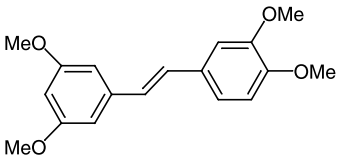
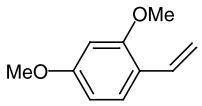
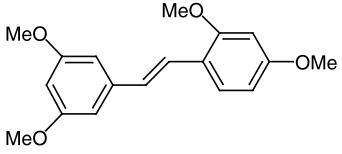
Entry	ArX	Styrene	Cat. (mol% Pd)	Reaction conditions[a]	*t*	Product	
						No.	Yield (%)[b]
1			**3a** (10^{-1})	Method A	14 h	**2a**	 99 [8.4:1] (77)
2			**3a** (1.1×10^{-2})	Method A	24 h	**2a**	77 [8:1]
3			$Pd(OAc)_2$ (1.1×10^{-2})	Method A	24 h	**2a**	88 [7.9:1]
4			**3a** (0.5)	Method A	14 h	**2a**	99 [10.5:1]
5			$Pd(OAc)_2$ (0.5)	Method A	14 h	**2a**	2
6			**3a** (0.5)	Method A[c]	10 min	**2a**	99 [6.3:1]
7			**3a** (1.1×10^{-2})	Method A	13 h	**2a**	96 [8.5:1] (85)
8			$Pd(OAc)_2$ (10^{-2})	Method A	13 h	**2a**	93 [10:1]
9			**3a** (10^{-2})	Method B	5 h	**2a**	95 [6:1]
10			$Pd(OAc)_2$ (10^{-2})	Method B	5 h	**2a**	99 [6.1:1]
11			**3a** (0.1)	Method C	23 h	**2a**	99 [9:1]
12			**3a** (0.15)	Method A	14 h	**2b**	 75 [14:1] (67)
13			**3a** (0.5)	Method A	8 h	**2b**	98 [16:1] (64)
14			**3a** (0.1)	Method A	14 h	**2c**	 98 [9.6:1] (75)
15			**3a** (0.1)	Method A	14 h	**2g**	 99 [4.2:1] (47)

Table 2 (*continued*)

Entry	ArX	Styrene	Cat. (mol% Pd)	Reaction conditions[a]	*t*	Product		
						No.		Yield (%)[b]
16			**3a** (0.1)	Method A	14 h	**2h**		99 [9.5:1] (86)
17			**3a** (0.1)	Method A	14 h	**2i**		99 [31:1] (94)

[a] Method A: DMA/H_2O (4/1), Cy_2NMe, TBAB, 120 °C (bath temperature). Method B: DMA, Et_3N, 120 °C (bath temperature). Method C: H_2O, Cy_2NMe, TBAB, 120 °C (bath temperature).

[b] Conversions determined by GC with decane as internal standard. In brackets, regioisomers ratio of crude product (determined by GC). In parenthesis, isolated yield of the (*E*)-stilbene **2** after flash chromatography (hexane/EtOAc).

[c] The reaction was performed under microwave irradiation conditions (120 W, 120 °C) at 0.5 mmol scale.

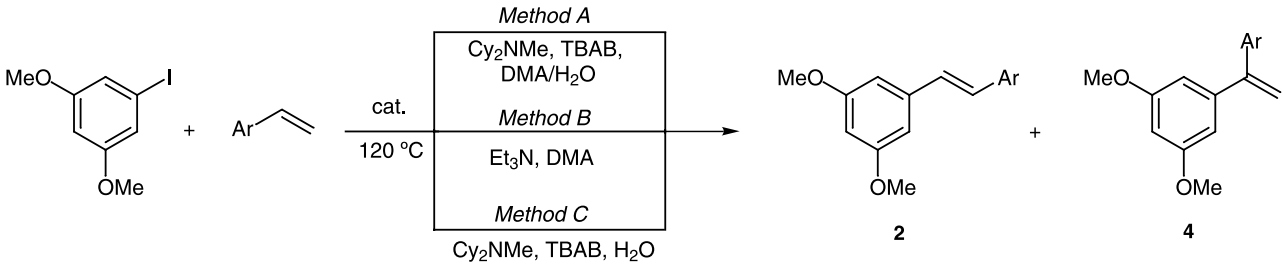
and 3,5-dimethoxyiodobenzene[31] as partners could be the most general strategy for combinatorial chemistry. However, for initial studies for methylated resveratrol (**2a**) two approaches were studied: (I) the arylation of 3,5-dimethoxystyrene[30,32] with 4-methoxyphenyl iodide and bromide and (II) the coupling of 4-methoxystyrene with 3,5-dimethoxyiodobenzene (Scheme 2 and Table 2). Both strategies gave good conversions when the reactions were performed following Method A–C (Table 2, entries 1–11) either under thermal or microwave conditions. There are some exceptions, such as using of $Pd(OAc)_2$ as catalyst the coupling of 4-methoxybromobenzene and 3,5-dimethoxystyrene failed (Table 2 entries 5) also under microwave conditions. The second strategy gave very low conversions under microwave conditions either with complex **3** or with $Pd(OAc)_2$ as catalysts.

Considering aryl iodides, strategy II occurred faster and with higher conversion than strategy I, it means that 3,5-dimethoxyiodobenzene is more reactive than 4-methoxyiodobenzene (Scheme 3, Table 2, compare entries 2 and 7 or 3 and 8). Following Method B (DMA, Et_3N) this second procedure occurred faster but with lower regioselectivity (Table 2, entries 9 and 10). Trimethylated resveratrol **2a** can also be prepared in water with (dicyclohexyl)methylamine as base and TBAB as additive (Method C) under thermal conditions although in longer reaction times than using Method A and B (Table 2, entry 11). However under microwave conditions the reaction took place with much lower conversion (20%). Conditions of Method A were used in the preparation of other methoxylated stilbenes because of the higher regioselectivity observed in the synthesis of resveratrol **2a**. In the case of stilbene **2b** 2-iodo and 2-bromothiophene were coupled efficiently with 3,5-dimethoxystyrene and with high regioselectivity (Table 2, entries 12 and 13, respectively).

For the rest of methoxylated stilbenes **2c**, **2g**–**2i**, 3,5-dimethoxyiodobenzene was coupled with the corresponding styrene (Scheme 3 and Table 2, entries 14–17). 2,4-Dimethoxystyrene[33] was prepared by Wittig reaction[30] and the rest of styrenes are commercially available. Compounds **2g** and **2i** along with **2a**–**c** present human cytochrome P450 1B1 inhibitory activity.[16] By demethylation of stilbenes **2a**, **2g** and **2h** by standard methods[19,24] natural products, such as resveratrol, piceatannol and pinosilvine, respectively can be obtained.

3. Conclusion

In conclusion, we have found appropriate reaction conditions to perform the Heck reaction between deactivated aryl halides and styrenes using oxime-derived palladacycle **3a** or $Pd(OAc)_2$ as catalysts in air and under phosphane and silver salt-free conditions. The reactions can be performed using (dicyclohexyl)methylamine in aqueous DMA or in neat water and TBAB as additive and in DMA with Et_3N as base. The former reaction conditions allowed the coupling between 3,5-dimethoxyiodobenzene and styrenes with the best regioselectivity. This methodology is an efficient regio and stereoselective way for the preparation of biologically active methoxylated stilbenes.



Scheme 3.

4. Experimental

4.1. General

All reagents and solvents were obtained from commercial sources and were generally used without further purification. Palladacycle **3** was purchased from MEDALCHEMY S. L. Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) in glass vessels (10 mL) sealed with a septum under magnetic stirring. The catalysts were weighed out in an electronic microscale (Sartorius, XM1000P) with a precision of 1 μg. Thin liquid chromatography for R_f was performed on Polygram® Silica Gel 60 UV_{254} plates, purchased from Merck. Mp were measured in a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on an HP-5890 instrument equipped with a WCOT HP-1 fused silica capillary column using decane as internal standard. IR data were collected on a Nicolet Impact 400D-FT. ^{1}H NMR spectra were recorded on a Bruker AC-300 MHz spectrometer and ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as the internal reference. Mass spectra (MS) were obtained at 70 eV on a Hewlett Packard HP 6890 series GC system with a 5973 network mass selective detector.

4.2. Heck reactions. General procedures for the preparation of compound 2

Method A. A 15 mL Ace pressure tube was charged with aryl halide (1 mmol), styrene (1.5 mmol), (dicyclohexyl)-methylamine (0.32 mL, 1.5 mmol), tetrabutylammonium bromide (0.32 g, 1 mmol), catalyst (0.1–0.5 mol % Pd), DMA (4 mL) and water (1 mL). Reactions with 10^{-2} mol % Pd were performed at 2 mmol scale with the same amount of solvents. The solution was stirred at 120 °C in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the reaction mixture was poured into ethyl acetate (20 mL) and washed with 2 M HCl (2×10 mL) and water (2×10 mL). The organic phase was dried over Na_2SO_4 and evaporated (15 Torr). The subsequent residue was purified by flash chromatography on silica gel to obtain the corresponding styrene. Only in the preparation of compound **2i**, the reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (2×15 mL). The combined organic phases were washed with aqueous saturated $NaHCO_3$ solution (3×10 mL), dried over Na_2SO_4 and evaporated (15 Torr) to obtain a residue which was purified by flash column chromatography on silica gel.

Method B. A 15 mL Ace pressure tube was charged with aryl halide (2 mmol), styrene (3 mmol), triethylamine (0.42 mL, 3 mmol), catalyst (10^{-2} mol% Pd) and DMA (3 mL). The solution was stirred at 120 °C in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped the same extractive work-up as before was performed.

Method C. A 15 mL Ace pressure tube was charged with aryl iodide (1 mmol), styrene (1.5 mmol), (dicyclohexyl)-methylamine (0.32 mL, 1.5 mmol), tetra-*n*-butylammonium bromide (0.32 mg, 1 mmol), **3a** (292 μg, 0.001 mmol Pd) and water (2 mL). The mixture was stirred at 120 °C in air and the reaction progress was analyzed by GC. After the reaction was completed or stopped, the same extractive work-up as before was performed.

All compounds have been previously reported and were characterized by comparison with their reported physical and spectroscopic data:

(*E*)-1-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-ethene (**2a**). Mp 53–56 °C (lit.[16] 55–57 °C).
(*E*)-1-(3,5-Dimethoxyphenyl)-2-(2-thiophenyl)ethene (**2b**).[16] Oil.
(*E*)-1-(3,4-Dimethoxyphenyl)-2-(3,5-dimethoxyphenyl)-ethene (**2c**). Mp 67–68 °C (lit.[16] 66–67 °C).
(*E*)-1,2-Di(4-chlorophenyl)ethene (**2d**). Mp 175–178 °C (lit.[34] 177–178 °C).
(*E*)-1-(4-Chlorophenyl)-2-(4-methoxyphenyl)ethene (**2e**). Mp 181–184 °C (lit.[35] 185 °C).
(*E*)-1-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-ethene (**2f**). Mp 136–138 °C (lit.[36] 133–135 °C).
(*E*)-1-(2,4-Dimethoxyphenyl)-2-(3,5-dimethoxyphenyl)-ethene (**2g**). Mp 82–83 °C (lit.[16] 78–79 °C).
(*E*)-1-(3,5-Dimethoxyphenyl)-2-phenylethene (**2h**). Mp 54–55 °C (lit.[37] 59–60 °C).
(*E*)-1-(3,5-Dimethoxyphenyl)-2-(4-pyridyl)ethene (**2i**). Mp 69–70[38] (lit.[16] 139–144 °C).

Acknowledgements

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38. This compound has been recrystallized several times and presented the same spectral data than in the literature,[16] its purity being higher than 99% by GC.

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9-BBN as a convenient protecting group in functionalisation of hydroxylysine

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Abstract—9-BBN was used for regioselective protection of the α-amino and α-carboxyl groups of (5*R*)-5-hydroxy-L-lysine. The resulting 9-BBN complex was then employed in transformations such as *N*-Cbz protection, azido transfer, *O*-glycosylation, and *O*-silylation. Further manipulations led to improved methods for preparation of hydroxylysine and galactosylated hydroxylysine building blocks, suitable for direct use in peptide synthesis under standard Fmoc conditions.

1. Introduction

Lysine residues in collagen can undergo post-translational hydroxylation to give (5*R*)-5-hydroxy-L-lysine, which was first discovered in protein hydrolysates.[1,2] In collagen, hydroxylysine residues are essential for the stability of intermolecular collagen cross-links.[3] In addition, hydroxylysine in collagen may be glycosylated, either with a β-D-galactopyranosyl- or an α-D-glucopyranosyl-(1→2)-β-D-galactopyranosyl moiety.[4] Recent studies have revealed that T cell hybridomas obtained in collagen-induced arthritis (CIA), which is a common mouse model for rheumatoid arthritis (RA), specifically respond to a galactosylated hydroxylysine residue located in a peptide fragment from type II collagen.[5,6] A dominance of T cell responses to such glycopeptides from type II collagen was also recorded in a cohort of severely affected RA-patients, suggesting a crucial role for the glycosylated form of hydroxylysine in development of RA in humans.[7]

(5*R*)-N^{α}-(Fluoren-9-ylmethoxycarbonyl)-N^{ε}-benzyloxycarbonyl-5-hydroxy-L-lysine allyl ester (cf. **6**, Scheme 1) is an important intermediate for preparation of glycosylated hydroxylysine building blocks for use in solid phase glycopeptide synthesis.[5,6,8–10] Previous procedures reported from our[8,9] and other laboratories[11] for synthesis of glycosylated derivatives of hydroxylysine have involved initial formation of a cupric chelate of hydroxylysine followed by regioselective protection of the N^{ε}-amino group. The procedure developed in our laboratory allowed conversion of hydroxylysine into building block **6** in approximately 30% overall yield,[8] but it involved some practical difficulties like tedious work up and isolation of intermediates and the final product. Consequently, there is a need for developing a more convenient and high-yielding procedure for regioselective protection and glycosylation of hydroxylysine. 9-Borabicyclononane (9-BBN) has recently been reported to be convenient for simultaneous protection of the carboxyl and amino functionalities of amino acids, thereby imparting solubility of the corresponding borane complexes in various organic solvents.[12,13] We therefore turned our attention towards investigating if 9-BBN can be used as protecting group for the α-amino acid moiety of hydroxylysine and if this allows functional group transformations of the amino and hydroxyl groups in the side chain.

2. Results and discussion

Commercially available (5*R*)-5-hydroxy-L-lysine dihydrochloride was first dissolved in aqueous ammonia. Concentration and drying under high vacuum gave a solid that was treated with a slight excess of 9-BBN in refluxing methanol to give the soluble borane complex **1** in quantitative yield (Scheme 1). Interestingly, formation of a 9-BBN complex involving the δ-hydroxyl and ε-amino groups was not detected, revealing a very high selectivity for protection of the α-amino acid functionality of hydroxylysine. Previous studies have indicated that 9-BBN protected amino acids are surprisingly tolerant to a wide range of reaction conditions.[12] In line with these observations protection of the N^{ε}-amino group of **1** with benzyl chloroformate gave the

Keywords: Hydroxylysine; 9-BBN; Boroxazolidinone complex; Glycosylation.
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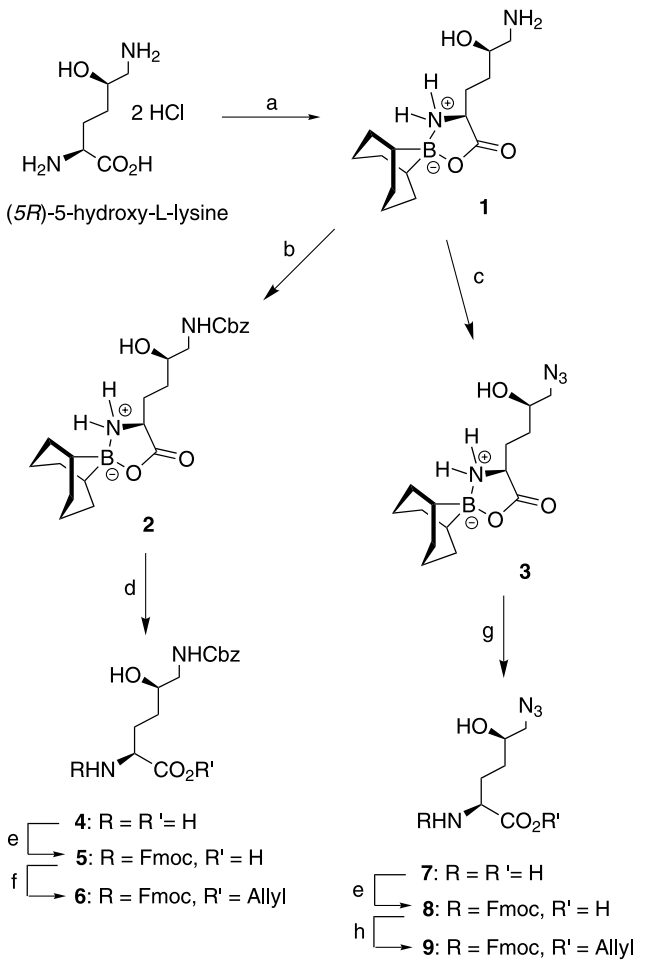
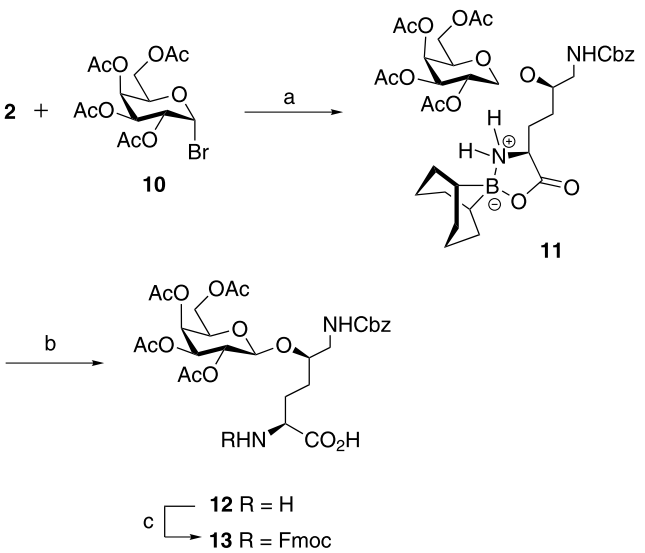


Scheme 1. (a) Aqueous NH_3 solution, 0 °C, 30 min, concentration, then 9-BBN, methanol, reflux, 4 h; (b) Cbz-Cl, $NaHCO_3$, dioxane–water, 0 °C→rt (92% yield from hydroxylysine); (c) TfN_3, K_2CO_3, $CuSO_4$, CH_2Cl_2, MeOH, 18 h, rt, (56%); (d) ethylenediamine, THF, reflux; (e) Fmoc-Cl, Na_2CO_3, dioxane–water, 1:1; (f) Cs_2CO_3, aq. EtOH, allyl bromide, DMF, rt (72% from **2**); (g) MeOH–HCl, rt, 10 min; (h) allyl alcohol, TMSCl, 0 °C→rt, 10 h (45% from **3**).

N^{ε}-Cbz protected borane complex **2** (92% yield from hydroxylysine), without any apparent reaction at the α-amino group. Complex **1** could also be treated with freshly prepared triflyl azide[14] in dichloromethane to give azido derivative **3** (56%).

Decomplexation of borane complex **2** to give **4** was obtained by heating with ethylene diamine in THF (Scheme 1). N^{α}-Fmoc protection of the α-amino group of **4** followed by conversion of the carboxyl group to an allyl ester via treatment of the corresponding cesium salt with allyl bromide in DMF yielded the differentially protected hydroxylysine derivative **6**[8] (72% from **2**). Compound **6** has previously been described as a key building block for preparation of galactosylated derivatives of (5*R*)-5-hydroxy-L-lysine, which were subsequently employed in solid-phase glycopeptide synthesis.[6,8–10] Decomplexation of azido derivative **3** was accomplished by using concentrated aqueous hydrogen chloride in methanol to give **7**. The α-amino group of **7** was then protected with an Fmoc group and the carboxyl group of **8** was converted into an allyl ester by treatment with trimethylsilyl chloride in allyl alcohol. This gave azido-hydroxylysine derivative **9** in 45% yield from **3**. Attempted glycosylation of **9** with 2,3,4,6-tetra-*O*-acetyl-galactosyl bromide as a glycosyl donor and silver silcate as a promotor failed. This was unexpected since these conditions give high and reproducible yields (appr. 80%) for the analogous Cbz-derivative **6**.[9] Efforts to perform the glycosylation using other glycosyl promoters, that is, ICl/AgOTf[15] or Br_2/AgOTf[16] proved futile and no product formation was observed. Somewhat surprisingly, it therefore had to be concluded that the azido-hydroxylysine derivative **9** is a poor glycosyl acceptor.

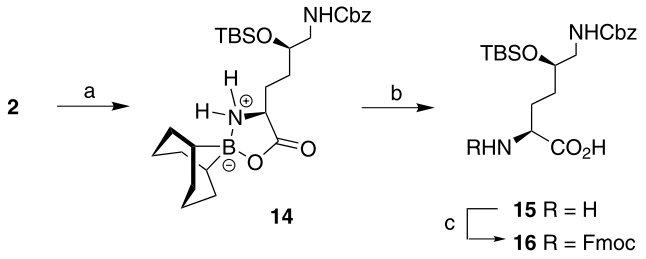
Due to our interest in developing a more efficient, reproducible and less time-consuming procedure for preparation of galactosylated hydroxylysine building blocks, glycosylation of the Cbz-protected hydroxylysine boroxazolidinone complex **2** was investigated. It was found that silver silicate promoted glycosylation of complex **2** with galactosyl bromide **10** in dichloromethane at 0 °C furnished the desired β-glycoside **11** in 68% yield (Scheme 2). Formation of detectable amounts of the corresponding α-anomer or orthoester, or decomposition of the 9-BBN complex, was not observed. The glycosylated borane complex **11** was stable to purification by column chromatography on silica gel and its identity was confirmed by NMR spectroscopy and LCMS. However, some decomposition of **11** to give the glycosylated amino acid **12** was observed upon prolonged standing of the fractions obtained after column chromatography with a mixture of chloroform and methanol as eluent. This serendipitous discovery provided a milder alternative for decomplexation[13] than those previously employed, that is, use of either ethylenediamine or concentrated HCl in methanol.[12] Such harsh conditions would have affected either the *O*-acetyl protective groups or the β-glycosidic linkage of **11**, respectively. Complete decomplexation was therefore achieved by treating **11** with a mixture of chloroform and methanol during 12 h at room temperature. Fmoc protection of **12** using 9-fluorenylmethoxycarbonyl-*N*-hydroxy-succinimide ester (Fmoc-OSu) and sodium bicarbonate as



Scheme 2. (a) Silver silicate/silver zeolite, CH_2Cl_2, 0 °C, 8 h (68%); (b) $CHCl_3$–MeOH, rt 12 h; (c) Fmoc-OSu, $NaHCO_3$, acetone–H_2O (91% from **11**).

base, followed by acidification, afforded the glycosylated hydroxylysine building block **13**[9] in 91% yield from **11**. Synthesis of **13** was thus achieved in only five steps, and 56% overall yield from hydroxylysine dihydrochloride. The present procedure is simpler to carry out than the one reported previously by us,[9] since tedious concentrations of aqueous solutions are avoided. In addition the overall yield from commercially available hydroxylysine is improved significantly.

Finally, conversion of boroxazolidinone **2** into a hydroxylysine building block for use in peptide synthesis was investigated. The hydroxyl group in the hydroxylysine part of **2** was protected to avoid potential lactonisation with the carboxyl group during peptide synthesis (Scheme 3). Protection was achieved by treatment of **2** with *tert*-butyldimethylsilyl triflouromethanesulfonate in the presence of 2,6-lutidine which furnished silyl ether **14** in 86% yield. Subsequent cleavage of the borane complex with a mixture of chloroform and methanol, as described above, followed by Fmoc protection of the α-amino group afforded the desired hydroxylysine building block **16** (89% from **14**). Building block **16** was thus prepared in five steps and 70% overall yield from hydroxylysine dihydrochloride.



Scheme 3. (a) TBSOTf, 2,6 lutidine, CH_2Cl_2, 0 °C, 2 h (86%); (b) $CHCl_3$–MeOH, rt; (c) Fmoc-OSu, $NaHCO_3$, acetone–H_2O (89% from **14**).

3. Conclusion

In conclusion, 9-BBN has been shown to be an efficient protective group for the amino acid moiety of (5*R*)-5-hydroxy-L-lysine. It was also demonstrated the 9-BBN complex of hydroxylysine is tolerant to several manipulations in the side-chain, that is, *N*-Cbz protection, azido transfer, *O*-glycosylation, and *O*-silylation. Finally, use of the 9-BBN complex of hydroxylysine allowed convenient and improved methods for preparation of hydroxylysine and galactosylated hydroxylysine building blocks to be developed. These building blocks are suitable for use in peptide and glycopeptide synthesis according to the Fmoc strategy, either in solution or on solid support.

4. Experimental

4.1. General

TLC was performed on Silica Gel 60 F_{254} (Merck) with detection by UV light or charring with anisaldehyde solution (anisaldehyde, H_2SO_4, acetic acid, ethanol). Flash column chromatography was performed on silica gel (Matrex, 60 Å, 35–70 μm, Grace Amicon) with solvents of HPLC grade, analytical grade or distilled technical grade. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are referenced to residual $CHCl_3$ (δ_H=7.27 ppm) and $CDCl_3$ (δ_C=77.0) for solutions in $CDCl_3$. Optical rotations were recorded on a Perkin Elmer 343 polarimeter. 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl bromide **10** was prepared from peracetylated galactose by treatment with HBr in HOAc/Ac_2O. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy and LC–MS. They were also characterized by high resolution mass spectrometry.

4.1.1. (5*R*)-*N*$^{\varepsilon}$-Benzyloxycarbonyl-5-hydroxy-L-lysinato-bicyclononylboron (2). Ammonia solution (aq. 10 mL) was added to (5*R*)-5-hydroxy-L-lysine dihydrochloride monohydrate (1 g, 3.94 mmol) at 0 °C. After stirring for 30 min the solution was concentrated and the crystalline solid was dried in high vacuum before further use. The solid was added in one portion to a stirred solution of 9-BBN (1.2 g, 4.7 mmol) in hot methanol (20 mL). The reaction mixture was refluxed (ca. 3 h) under nitrogen until a clear solution was obtained. After evaporation of the solvent the residue was dissolved in hot THF and filtered. The filtrate was concentrated and the residue triturated with hot hexanes and finally with diethyl ether. The residue was dried under high vacuum to give crude **1** as an amorphous solid which was used as such in the next reaction. Sodium bicarbonate (0.50 g, 5.90 mmol), followed by Cbz-Cl (0.66 mL, 4.72 mmol), was added to a solution of **1** in a mixture of dioxane–water (1:1, 10 mL) at 0 °C. The reaction mixture was stirred for 5 h at rt and then concentrated. The compound was extracted by ethyl acetate (2×25 mL) from water (2×25 mL). The combined organic phases were washed once with brine (20 mL), water (25 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography using hexane–ethyl acetate as eluent to afford **2** (1.51 g, 92% yield) as a white amorphous solid: $[\alpha]_D^{20}=-14.8$ (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.53 (brd, 2H, *J*=10.7 Hz, (B-(C*H*)$_2$), 1.30–1.89 (m, 15H, B-(CH_2)$_6$, H-β, H-γ′, H-γ), 1.92–2.07 (m, 2H, H-β, –OH), 3.01–3.13 (m, 1H, H-ε), 3.15–3.26 (m, 1H, H-ε′), 3.62–3.71 (m, 1H, H-δ), 3.74 (m, 1H, H-α), 4.95–5.07 (m, 2H, PhCH_2), 5.18 (br s, 1H, N–Hα), 5.66 (m, 2H, N–Hα′, N–Hε), 7.22–7.33 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.1, 21.0, 22.8, 23.8, 24.3, 26.8, 29.8, 31.1, 31.2, 31.7, 46.6, 55.1, 60.4, 67.0, 70.8, 125.2, 127.9, 128.2, 128.2, 128.5, 129.0, 136.1, 157.7, 171.3, 175.3; HR-MS (FAB): calcd for $C_{22}H_{33}BN_2O_5$ 439.2375 $[M+Na]^+$, found 439.2410.

4.1.2. (5*R*)-5-Hydroxy-6-azido-L-lysinato-bicyclononylboron (3). *Preparation of triflyl azide*.[14] Dichloromethane (10 mL) was added to an ice cold solution of sodium azide (2.5 g, 38.4 mmol) in water (6.5 mL). The biphasic mixture was stirred vigorously and treated dropwise with triflic anhydride (1.2 mL, 7.8 mmol), over a period of 5 min. The reaction mixture was stirred for 2 h at 0 °C after which the organic phase was separated and the aqueous phase was extracted twice with dichloromethane (2×5 mL). The combined organic phases were washed with aqueous sat. sodium carbonate solution and the resulting triflyl azide solution was used without concentration in the next step.

Potassium carbonate (0.80 g, 5.85 mmol), $CuSO_4$ monohydrate (6 mg, 0.024 mmol), and triflyl azide solution prepared as above were added to a solution of crude borane complex **1** (1.1 g, 3.89 mmol) in methanol (25 mL). The reaction mixture was stirred for 18 h at rt and concentrated. The residue was extracted by ethyl acetate (20 mL) from water (15 mL) and the organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography using $CHCl_3$–MeOH (19:1) as eluent to afford azido derivative **3** (0.67 g, 56%) as a yellow amorphous solid: $[\alpha]_D^{20}=-10.2$ (*c* 1.7, MeOH); IR (neat, cm^{-1}): 840, 960, 1214, 1261, 1357, 1450, 1697, 2098, 2842, 2919, 3114, 3222; ^1H NMR ($CDCl_3$+MeOH-d_4, 400 MHz): δ 0.56 (br s, 2H, B-$(CH)_2$), 1.35–1.88 (m, 15H, B-$(CH_2)_6$, H-β, H-γ, H-γ′), 2.03–2.17 (m, 2H, H-β′, –OH), 3.26 (dd, 1H, *J*=7.6, 12.2 Hz, H-ε), 3.38 (dd, 1H, *J*=3.6, 12.4 Hz, H-ε′), 3.77–3.84 (m, 1H, H-δ), 3.85–3.93 (m, 1H, H-α), 5.23 (dd, 1H, *J*=8.0, 12.4 Hz, –NH), 5.56 (dd, 1H, *J*=8.2, 12.4 Hz, –NH); ^{13}C NMR ($CDCl_3$+MeOH-d_4, 100 MHz): δ 23.6, 24.1, 26.4, 29.2, 30.8, 30.8, 31.0, 31.1, 54.7, 56.5, 69.7, 127.8, 128.7, 175.3; HR-MS (FAB): calcd for $C_{14}H_{27}BN_4O_3$ 309.2092 $[M+H]^+$, found 309.2103.

4.1.3. (5*R*)-*N*$^{\alpha}$-(Fluoren-9-ylmethoxycarbonyl)-*N*$^{\varepsilon}$-benzyloxycarbonyl-5-hydroxy-L-lysine allyl ester (6). Excess ethylenediamine (1 mL, 16 mmol) was added to a solution of **2** (1.51 g, 3.62 mmol) in THF (5 mL) at room temperature and heated for 1 min. The suspension was cooled and filtered. The precipitate was washed with an additional amount of THF (15 mL) and dried in vacuo to afford crude **4** (0.95 g) which was used as such for the next step. A solution of 9-fluorenylmethyl chloroformate (1.25 g, 4.84 mmol) in dioxane (5 mL) was added dropwise to a solution of **4** in dioxane–10% Na_2CO_3 (15 mL, 1:2) at 0 °C. The solution was stirred for 5 h at rt and the dioxane was evaporated. Chloroform (20 mL) was added and the mixture was acidified to pH 2 with a 1 M solution of $KHSO_4$ at 0 °C. The organic phase was separated and the aqueous phase was extracted with an additional amount of chloroform (2×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford acid **5** (1.53 g). Aqueous Cs_2CO_3 was added to a solution of **5** in aqueous ethanol (80%) so that the pH was adjusted to 7. The solution was concentrated after stirring for 2 h. Allyl bromide (0.73 g, 5.43 mmol) was added to a solution of the resulting cesium salt in DMF (5 mL) and stirred for 12 h under nitrogen. The mixture was diluted with water and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), concentrated and the residue was purified by column chromatography over silica gel using heptane–ethyl acetate as eluent to afford allyl ester **6** (1.45 g, 72% for three steps). Compound **6** had ^1H and ^{13}C NMR data identical to those reported previously.[8]

4.1.4. (5*R*)-*N*$^{\alpha}$-(Fluoren-9-yl-methoxycarbonyl)-6-azido-5-hydroxy-L-lysine allyl ester (9). Concentrated aqueous HCl (2 mL) was added to a solution of **3** (0.67 g, 2.14 mmol) in methanol (5 mL) at 0 °C. The solution was stirred for 10 min at rt and then concentrated. The residue was triturated with hot hexanes and finally with ether. It was dried under high vacuum to afford crude **7** (0.36 g) which was used as such in the next step. A solution of 9-fluorenylmethyl chloroformate (0.631 g, 2.44 mmol) in dioxane (2 mL) was added dropwise to a solution of crude **7** (0.36 g) in dioxane–10% Na_2CO_3 (6 mL, 1:2) at 0 °C. The solution was stirred for 4 h at room temperature and the dioxane was evaporated. Chloroform (15 mL) was added and the mixture was acidified to pH 2 with a 1 M solution of $KHSO_4$ at 0 °C. The organic phase was separated, and the aqueous phase extracted with an additional amount of chloroform (2×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford crude acid **8** (0.58 g). Trimethylsilyl chloride (0.38 mL, 3.0 mmol) was added dropwise to an ice cold solution of crude **8** (0.58 g) in allyl alcohol (5 mL) under nitrogen. After stirring for 10 h at rt the solvent was evaporated and the residue was purified by flash column chromatography using hexane–ethyl acetate as eluent to afford the ester **9** (0.45 g, 45% over three steps). $[\alpha]_D^{20}=+0.58$ (*c*=2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.48–1.61 (m, 2H, H-γ, γ′), 1.70–1.83 (m, 1H, H-β), 1.99–2.11 (m, 1H, H-β′), 2.16–2.56 (br s, 1H, –O*H*), 3.18–3.37 (2 m, 2H, H-ε, ε′), 3.71–3.82 (m, 1H, H-δ), 4.21 (t, 1H, *J*=7.0 Hz, Fmoc-C*H*), 4.35–4.50 (m, 3H, Fmoc-CH_2, H-α), 4.64 (d, 2H, *J*=5.3 Hz, allylic CH_2), 5.29 (ddd, 2H, *J*=17.8, 10.6, 30.2 Hz, =CH_2), 5.55 (d, 1H, *J*=7.6 Hz, N–H), 5.82–5.95 (m, 1H, –C*H*=), 7.30 (t, 2H, *J*=7.5 Hz, Fmoc), 7.39 (t, 2H, *J*=7.3 Hz, Fmoc), 7.58 (d, 2H, *J*=7.1 Hz, Fmoc), 7.75 (d, 2H, *J*=7.4 Hz, Fmoc); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 20.5, 20.8, 21.4, 23.1, 23.9, 24.3, 26.5, 29.0, 31.0, 31.3, 31.3, 31.8, 44.1, 55.5, 61.7, 66.9, 67.0, 69.0, 70.5, 71.0, 81.4, 101.4, 125.2, 128.0, 128.2, 128.2, 128.4, 128.6, 129.0, 129.0, 136.2, 137.8, 157.1, 170.2, 170.2, 170.4, 173.5; IR (neat, cm^{-1}): 742, 1267, 1450, 1525, 1710, 2100, 2927, 3330; MS: HR-MS (FAB): calcd for $C_{24}H_{26}N_4O_5$ 450.1903 $[M+H]^+$, found 450.1898.

4.1.5. (5*R*)-*N*$^{\varepsilon}$-Benzyloxycarbonyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-5-hydroxy-L-lysinato-bicyclononylboron (11). A solution of acetobromo galactose (**10**, 1.45 g, 3.53 mmol) in dichloromethane (5 mL) was added dropwise to a stirred solution of **2** (1.02 g. 2.35 mmol) in dichloromethane (10 mL) containing silver silicate (3.2 g) and powdered molecular sieves (3 Å, 0.5 g) in the absence of light at 0 °C. The reaction mixture was stirred overnight under nitrogen at 0 °C. It was filtered and the filterate was concentrated. The residue was purified by flash column chromatography using toluene-acetonitrile as eluent to yield **11** (1.24 g, 68%) as a white amorphous solid. $[\alpha]_D^{20}=+4.9$ (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 0.55 (br s, 2H, (B-(C*H*)$_2$), 1.37–1.92 (m, 16H, B-$(CH_2)_6$, H-β, β′, H-γ, γ′), 1.95 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 3.30 (m, 2H, H-ε, H-ε′), 3.56–3.71 (m, 2H, H-δ, H-α), 3.82 (t, *J*=6.1 Hz, 1H, H-5), 4.03 (dd, 1H, *J*=7.5, 11.4 Hz, H-6), 4.14 (dd, 1H, *J*=5.4, 11.5 Hz, H-6′), 4.45 (d, 1H, *J*=8.0 Hz, H-1), 4.75–4.92 (m, 1H, NH-α), 4.97 (dd, 1H, *J*=3.3, 10.5 Hz, H-3), 5.07–5.14 (m, 4H, PhCH_2, H-2, NH-α′), 5.35 (d, 1H, *J*=3.0 Hz, H-4), 5.61 (t, 1H, *J*=6.1 Hz, N–Hε), 7.28–7.39 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.4, 20.7, 21.3, 23.0, 23.8, 24.3, 26.4, 28.9, 31.0, 31.2, 31.3, 31.7, 44.1, 55.5, 61.7, 66.9, 67.0, 68.9, 70.4, 71.0, 81.3, 101.4, 125.2, 128.0, 128.1, 128.3, 128.6, 128.9, 136.1, 137.8, 157.1, 169.9, 170.0, 170.2, 173.5; HR-MS (FAB): calcd for $C_{36}H_{51}BN_2NaO_{14}$ 769.3326 $[M+Na]^+$, found 769.3347.

4.1.6. (5*R*)-*N*$^{\alpha}$-(Fluoren-9-ylmethoxycarbonyl)-*N*$^{\varepsilon}$-benzyloxycarbonyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-5-hydroxy-L-lysine (13). Compound **11** (1.24 g, 1.66 mmol) was dissolved in methanol (2 mL) and diluted with chloroform (10 mL). The solution was stirred at room temperature for 12 h, and concentrated. The residue was triturated with hot hexanes and finally with diethyl ether (20 mL). It was dried in vacuo to afford crude **12**. A solution of 9-fluorenylmethoxycarbonyl-*N*-hydroxysuccinimide ester (Fmoc-OSu, 0.68 g, 2 mmol) in acetone (4 mL) was added to a solution of **12** and $NaHCO_3$ (0.152 g, 1.82 mmol) in water (10 mL). The mixture was stirred at room temperature for 5 h and concentrated. Chloroform was added and the mixture was acidified to pH 2 with dilute aqueous HCl at 0 °C. The compound was extracted twice with an additional amount of chloroform (2×15 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography using toluene–ethanol (30:1→10:1→4:1) as eluent to afford **13** (1.28 g, 91% over two steps). Compound **13** had ^{1}H and ^{13}C NMR data identical to those reported previously.[9]

4.1.7. (5*R*)-*N*$^{\varepsilon}$-Benzyloxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-L-lysinato-bicyclononylboron (14). 2,6-Lutidine (0.16 mL, 1.38 mmol) followed by *tert*-butyldimethylsilyl triflouromethanesulfonate (0.19 mL, 0.83 mmol) was added to a stirred solution of **2** (0.30 g, 0.72 mmol) in dichloromethane (2 mL) at 0 °C under nitrogen. After 2 h, diethylether was added and the solution was washed with water (5 mL) followed by aqueous sat. NaCl (5 mL). The organic layer was dried (Na_2SO_4), concentrated and the residue purified by flash column chromatography using toluene–acetonitrile as eluent to afford **14** (0.32 g, 86%) as a yellow oil that solidified upon standing. $[\alpha]_D^{20}$=+5.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.51, 0.61 (br s, each 1H, B-(C*H*)$_2$), 0.87 (s, 9H, $Si(CH_3)_3$), 1.35–1.97 (m, 15H, $B(CH_2)_6$, H-β, H-β′, H-γ), 2.10–2.24 (m, 1H, H-γ′), 3.02–3.14 (m, 1H, H-ε), 3.25–3.37 (m, 1H, H-ε′), 3.54–3.65 (m, 1H, H-α), 3.67–3.76 (m, 1H, H-δ), 4.59 (dd, *J*=8.1, 11.4 Hz, 1H, NH-α), 4.87 (dd, *J*=7.4, 11.2 Hz, 1H, NH-α′), 5.07 (d, *J*=6.0 Hz, 2H, PhC*H*$_2$), 5.14 (t, *J*=6.2 Hz, 1H, NH-ε), 7.27–7.39 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.6, −4.8, 18.1, 20.6, 23.9, 24.3, 25.8, 26.9, 31.0, 31.3, 32.1, 44.6, 55.5, 67.1, 70.8, 127.6, 128.3, 128.7, 136.3, 157.8, 173.1; HR-MS (FAB): calcd for $C_{28}H_{48}BN_2O_5Si$ 531.3420 $[M+H]^+$, found 531.3427.

4.1.8. (5*R*)-*N*$^{\varepsilon}$-Benzyloxycarbonyl-*N*$^{\alpha}$-(fluoren-9-ylmethoxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-L-lysine (16). Compound **14** (0.32 g, 0.60 mmol) was converted to crude **15** using a mixture of $CHCl_3$–MeOH as described above in the synthesis of **13**. Treatment of crude **15** with Fmoc-OSu (0.24 g, 0.72 mmol) and $NaHCO_3$ (0.055 g, 0.663 mmol), as described for the preparation of **13**, gave **16** (0.34 g, 89%) as a white amorphous solid after purification by flash column chromatography using toluene–acetonitrile as eluent. $[\alpha]_D^{20}$=+6.1 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.60 (m, 2H, H-γ), 1.72 (m, 1H, H-β), 1.94 (m, 1H, H-β), 3.15–3.44 (m, 2H, H-ε), 3.60–3.82 (m, 1H, H-δ), 4.20 (t, 1H, *J*=7.0 Hz, Fmoc-C*H*), 4.25–4.50 (m, 2H, Fmoc-C*H*$_2$), 5.01–5.22 (m, 3H, PhC*H*$_2$, NH), 5.59 (br s, 1H, NH), 5.76 (1H, d, *J*=7.6 Hz, H-α), 7.20–7.42 (m, 9H, Ph, Fmoc), 7.50–7.65 (m, 2H, Fmoc), 7.71–7.80 (d, 2H, *J*=7.2 Hz, Fmoc), 9.8 (br s, 1H, COOH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ −4.6, −4.5, 18.1, 25.7, 26.0, 29.9, 30.4, 63.8, 66.1, 67.3, 69.7, 115.6, 119.4, 120.0, 125.1, 126.0, 127.1, 127.7, 128.2, 128.5, 129.3, 132.0, 137.1, 141.3, 143.6, 143.7, 157.8, 168.9, 175.7; MS: HR-MS (FAB): calcd for $C_{35}H_{45}N_2O_7Si$ 633.2991 $[M+H]^+$, found 633.3000.

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Studies towards the total synthesis of contignasterol

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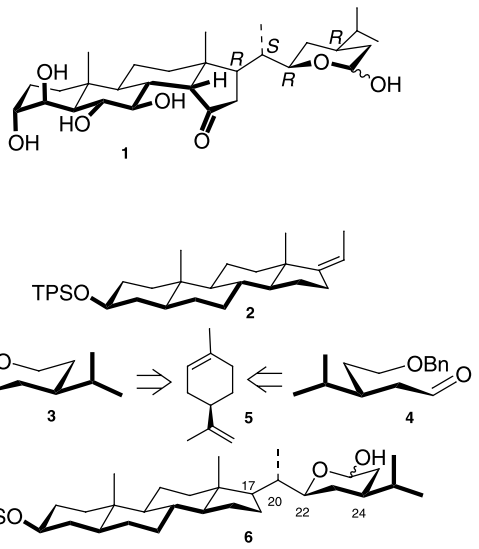
Abstract—The (17*R*,20*S*,22*S*,24*S*) $C_{20}-C_{29}$ segment of contignasterol has been stereoselectively prepared in 8 steps and 40% overall yield from (*S*)-carvone. Synthetic studies towards contignasterol's C/D ring functionalization/isomerization are also reported.

1. Introduction

Marine sponges have proven to be a rich source of novel steroids showing potent biological activities and unusual structural features.[1] Contignasterol[2] (**1**), 15-dehydro-14β-anosmagenin,[3] xestobergsterols A–C,[4] haliclostanone sulfate,[5] 14β-tamosterone sulfate[6] and clathriol[7] present common 15-keto, 3α(or β),6α,7β-trihydroxy functionalities and a rare *cis* C/D ring junction. This last feature is probably associated with potent antiiflammatory activity[8] as shown by Jung and Johnson's[9] brilliant synthesis of xestobergsterol A and its analogs.

In a previous work on the synthesis of contignasterol's side chain, we indicated as (*S*,*S*) the configuration for the C-22/C-24 stereogenic centres.[10] On the other side, 1 year after the publication of our results, Andersen and Yang[11] completed contignasterol's structural elucidation and, on the basis of a ^{1}H NMR spectroscopic data analysis of C-22 (*R*/*S*)-MPA and (*R*/*S*)-MTPA esters, proposed a (22*R*,24*R*) configuration. In the authors' opinion the synthesis-based C22/24 antipodal assignment was due to the unfunctionalized *trans* C/D tetracyclic nucleus model, which is 'an unreliable predictor of the side chain stereochemistries'.[11]

As a prelude to the contignasterol total synthesis and with the aim of shedding light on this open question, herein we report a new, shorter and higher yielding route for the (17*R*,20*S*,22*S*,24*S*)-$C_{20}-C_{29}$ fragment and our studies towards the C/D ring functionalization/isomerization.



2. Results and discussion

2.1. New route to contignasterol's side chain

Our first synthesis of contignasterol's (17*R*,20*S*,22*S*,24*S*)-side chain[10] relied on a stereospecific pericyclic coupling between the protected (*Z*)-17(20)-ethylidene steroid **2** and partner pseudo-enantiomeric aldehydes **3** and **4**, both available from (*R*)-limonene (**5**). The synthesis of **6** was thus completed in 12 steps and 11% overall yield.

In this paper we wish to report full experimental details of a more convenient route towards **6**. This synthesis, based on intermediate **7**, gave the lactol **6** in 8 steps and 40% overall yield starting from (*S*)-carvone.[12]

Keywords: Contignasterol; Polyhydroxysteroids; Marine metabolite; *anti*-Inflammatory compounds; Ene reactions.
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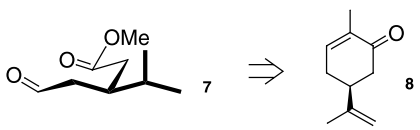
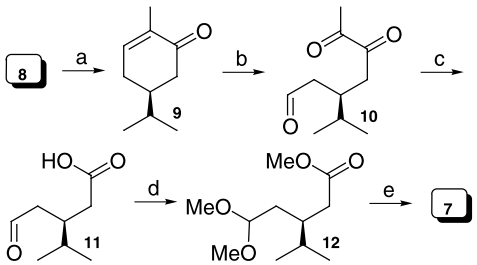
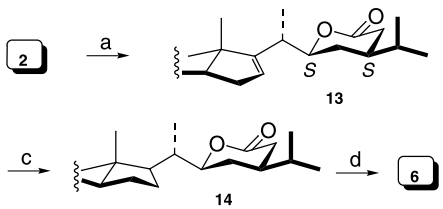


Elaboration of (*S*)-methyl 4-methyl-3-(2-oxo-ethyl)-pentanoate (**7**), reported in Scheme 1, began with a chemoselective reduction of (*S*)-carvone's isopropylidene double bond.[13] Carvotanacetone (**9**) was then converted, via ozonolysis,[13] $NaIO_4$-mediated oxidative cleavage,[13] and treatment with catalytic amount of *p*-TsOH in MeOH, into the air-stable acetal ester **12** (59% overall yield). When needed the aldehyde **7** was obtained through facile Pd(II)-mediated acetal hydrolysis.[14]



Scheme 1. (a) H_2, Pt_2O, MeOH; (b) O_3, MeOH, −60 °C then Me_2S, H_2O, MeOH; (c) $NaIO_4$, MeOH, H_2O; (d) MeOH, *p*-TsOH (59%, 4 steps); (e) $Pd(MeCN)_2Cl_2$, acetone/H_2O (95:5), 82%.

The (17*R*,20*S*,22*S*,24*S*)-side chain stereogenic centres, present in **6**, were stereoselectively forged starting from Koreeda's coupling.[15] This pericyclic reaction gave, without detectable stereoisomeric contamination, the expected lactone **13**.[16] Δ^{16} stereoselective hydrogenation[17] and DIBAL-H mediated C-29 reduction, furnished known[10] lactol **6** (Scheme 2).



Scheme 2. (a) **7**, Me_2AlCl, CH_2Cl_2, −78 °C→−30 °C, 90%; (b) H_2, Pt_2O, EtOH, quant.; (c) DIBAL-H, CH_2Cl_2, −78 °C, 93%.

2.2. Studies towards C/D ring functionalization

A number of synthetic methods useful for allylic oxidation of unsaturated steroids have been reported.[18] Among these the chromium trioxide 3,5-dimethylpyrazole-complex (CrO_3-DMP) mediated[19] C-15 allylic oxidation gave good results. This reaction, when applied to **13**, afforded the Δ^{16}-15-ketosteroid **15** in a satisfying yield (60%), along with the 16α,17α-epoxide **16**[20] (11% yield).

The *trans* C/D ring junction present in steroid **15** showed a slow but irreversible C-14 inversion ($t_{1/2}\approx$5 h, $CDCl_3$) to give the *cis* C/D steroid **17**.[21] Assignment of the C/D ring junction was made on the basis of the H-7 and C-18 NMR spectroscopy chemical shifts values (^{1}H NMR: $\delta_{H\text{-}18}$=0.98 for **15** versus $\delta_{H\text{-}18}$=1.18 for **17**, $\delta_{H\text{-}7\beta}$=2.63 for **15**, $\delta_{H\text{-}7\alpha}$=2.17 for **17**; ^{13}C NMR: $\delta_{C\text{-}18}$=23.5 for **15** versus $\delta_{C\text{-}18}$=24.4 for **17**).[22] Semiempirical calculations at the AM1 level, using the Gaussian 98W software package,[23] on compounds **15** and **17**, in which the TPS group was replaced by a methyl, provided the two minimum energy conformers **18a** and **18b** respectively (Fig. 1). In particular, the *cis* C/D ketone **18b** was shown to be more stable than the *trans* C/D ketone **18a** by approximately 5.1 kcal/mol, a value which is in full accordance with the irreversible C-14 inversion.

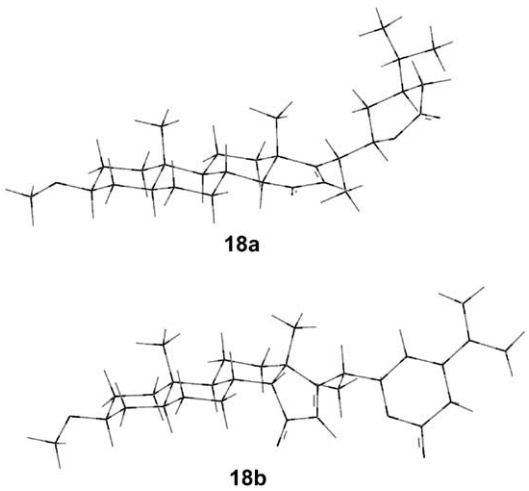


Figure 1. Minimum energy conformation for **18a** and **18b**, as determined by AM1 calculations.

Experimentally, the C-14 epimerization was complete in 24–30 h and served as point of departure for projected Δ^{16} reduction. Unfortunately, as a consequence of the conformation assumed by the unsaturated D ring,[17b,24] the hydrogenation gave quantitative yields of **19**, which, as clarified by a ROESY[25] experiment (Fig. 2), showed an unnatural C-17α (17*S*) side chain. Indeed, ROE cross-peaks

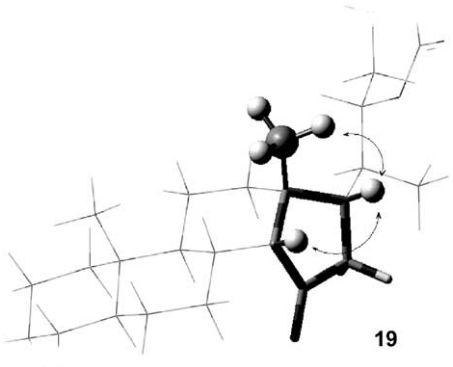
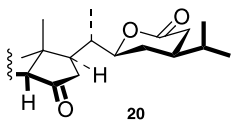


Figure 2. AM1 minimum energy conformation for **19**, in agreement with ROE cross-peaks between the H-17 with both H_3-18 and H-14.

between the H-17 (δ=1.80) with both H_3-18 (δ=1.02) and H-14 (δ=1.54), are in accordance with the distances of 2.98 and 2.70 Å, respectively, which were in turn measured in the AM1 minimum energy conformer of **19**.

In order to ensure a β-selective Δ^{16}-hydrogenation, we subjected the *trans* C/D α,β-unsaturated ketone steroid **15** to an acid-free hydrogenation, immediately after its oxidative formation. This time the reduction furnished, in excellent yield (95%), a *trans* C/D ring (^{13}C NMR: $\delta_{C\text{-}18}$=12.9, ^{1}H NMR: $\delta_{H\text{-}18}$=0.79) (17*R*)-steroid **20**.



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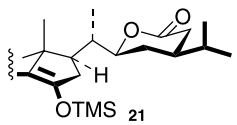
With (17*R*,20*S*,22*S*,24*S*)-**20** in hand, we were ready for the required C/D ring junction inversion.[26] The lability of the lactone excluded a base-induced isomerization. On the other side, the attempted acid catalyzed (HCl) C-14 inversion proved unsuccessful. Alternatively, we planned the formation of silyl enol ether **21**, in the presence of 1,1,1,3,3,3-hexamethyldisilazane and LiI, under thermodynamic control, and its protonation with trifluoroacetic acid, but, when we performed the acid-mediated hydrolysis of the silyl enol ether **21**, no trace of the 14β-H 15-ketosteroid was observed in the crude reaction mixture.



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At this point, considering the base-mediated C-14 inversion to be inevitable, we decided to transform the lactone moiety, into the base-stable C-29 acetal. Preliminary calculations (Fig. 3) on two steroid models, with an equatorial *O*-methyl acetal, showed contrasting results with regard to the relative stability of *trans* C/D ring steroid **22a** and the corresponding *cis* 15-ketosteroid **22b**. In fact, while AM1 calculations indicated the *cis* 15-ketosteroid **22b** to be more stable by about 2.5 kcal/mol with respect to the *trans* C/D ring steroid **22a**, PM3 calculation suggested a comparable stability.

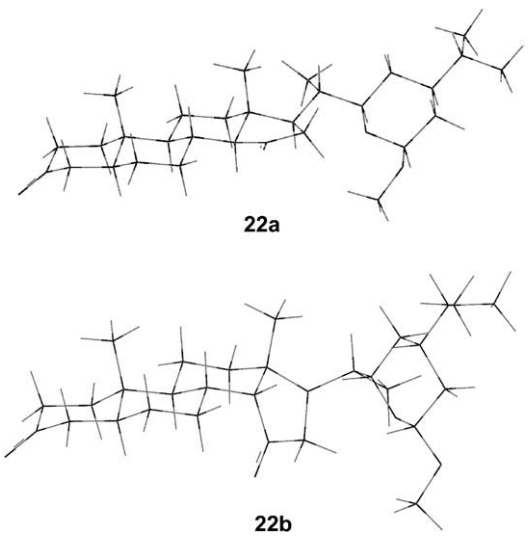
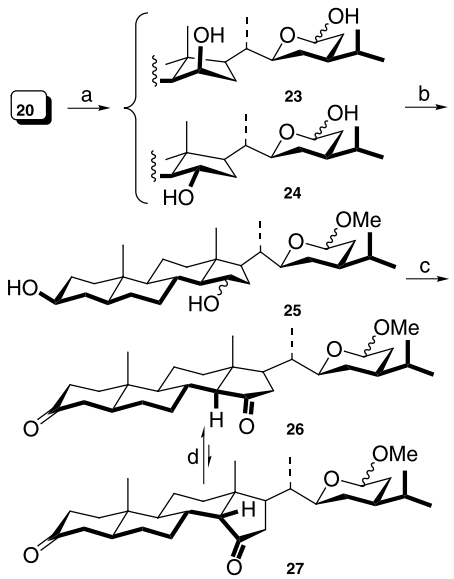


Figure 3. Minimum energy conformation for **22a** and **22b**, as determined by molecular mechanics calculation.

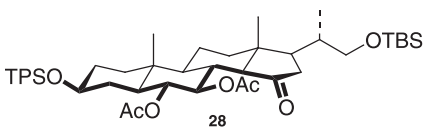
We thus reduced both the C-15 and C-29 carbonyls of **20** with DIBAL-H and separated (only for analytical purposes) the two epimeric C-15 alcohols **23** and **24**[27] (Scheme 3). Acid-mediated *O*-methylation of the mixture containing the C-15/C-29 epimers, furnished the four acetals **25** (the acid conditions deprotected the C-3 hydroxy group). Oxidation with PDC gave the expected 3,15-diketone **26** which, after treatment with different bases (MeONa, NaH, NaOH) at different temperatures and reaction times[28] did not show any C-14 isomerization.



Scheme 3. (a) DIBAL-H, CH_2Cl_2, −78 °C (**23**: 48%; **24**: 38%); (b) HCl in MeOH; (c) PDC, CH_2Cl_2, 55%, for 2 steps; (d) MeONa, MeOH, rt→reflux or NaH, THF, rt→reflux or NaOH, THF/EtOH, rt→reflux.

Having verified the difficulties in obtaining the required *cis* C/D ring junction with simpler model steroids, we decided to 'invest' in the known destabilizing influence exerted by the 7β-oxysubstituents on *trans* C/D ring junction.[9a] We thus projected the synthesis of 6α,7β-(diacetoxy)-22-[(*tert*-butyldimethylsilyl)oxy]-3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorcholan-15-one (**28**) with the aim to obtain a suitable substrate for the necessary C-14 inversion.

AM1 energy calculations on 7β-acetoxy *trans* C/D model steroid **28a** and 7β-acetoxy *cis* C/D **28b** showed that the former is less stable than the latter of about 5.5 kcal/mol, thus indicating the unfavourable steric interaction between the 7β-substituent and the C-15 keto group in *trans* C/D steroids, also accompanied, for structure **28a**, by a distortion of ring B from a pure chair conformation. This strain could be alleviated once the C-14/C-15 bond assumes the quasi-axial orientation present in *cis* C/D steroids (Fig. 4).



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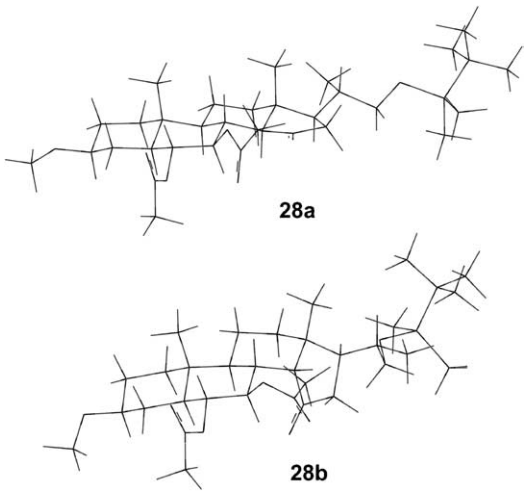
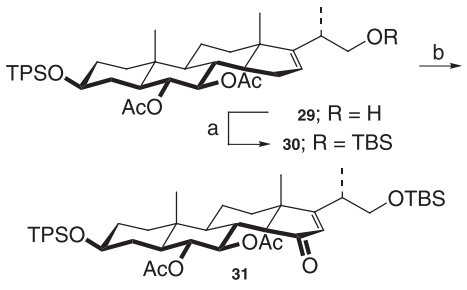


Figure 4. AM1 minimum energy conformations for **28a** and **28b**.

We thus embarked in the synthesis of the previously reported[29] 6α,7β-(diacetoxy)-3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-22-ol (**29**). Its construction was complete in 13 steps and 21% overall yield, starting from commercially available androst-5-en-3β-ol-17-one. Silylation of the primary C-22 alcohol with *tert*-butyldimethylsilyl chloride, gave the fully protected tetrol **30** (Scheme 4). This was subjected to both chromium,[19] copper,[18e] and selenium-mediated[18a] oxidation reactions (see Section 4) but, even forcing the reaction conditions, we did not observe the desired C-15 oxidation.[30]



Scheme 4. (a) TBSCl, DBU, CH_2Cl_2, 82%. (b) CrO_3-DMP, CH_2Cl_2 or SeO_2, *t*-BuOOH, CH_2Cl_2 or CuI, *t*-BuOOH, CH_3CN.

The analysis of the AM1 minimum energy conformer of **30a** (Fig. 5), in which the TPS group of **30** was replaced by a methyl, may suggest a steric hindrance of the 7β-acetoxy towards the access to C-15 which could prevent the oxidation reaction.

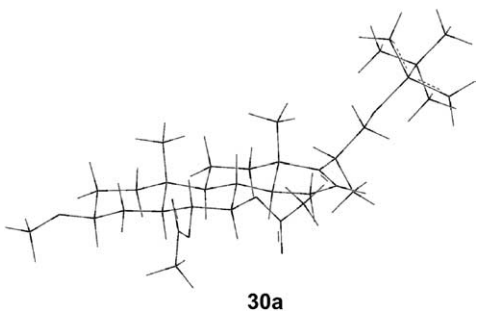


Figure 5. AM1 minimum energy conformations for **30a**.

At the end of this synthetic effort we assumed that the C-15 oxidation was incompatible with the presence of a 7β-oxysubstituent[31] and that, the only possible C-15 functionalization/C-14 isomerization route could be that starting from the Breslow remote functionalization (compatible with a 7β-oxysubstituent).[9a]

3. Conclusions

In conclusion, we have reported full experimental details of a new and more convenient route towards contignasterol's side chain and a synthetic and theoretical contribution for the C-15 oxidation/C-14 isomerization of contignasterol.

4. Experimental

4.1. General methods

All reactions were carried out under a dry argon atmosphere using freshly distilled and dried solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Toluene, methylene chloride and diethyl ether were distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried in vacuo over P_2O_5 or by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and sprying with H_2SO_4–$Ce(SO_4)_2$, *p*-anysaldeyde–EtOH–H_2SO_4–AcOH solutions and drying.

Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure materials. The NMR spectra were recorded at room temperature on a Bruker DRX 400 spectrometer (400 MHz) and ^1H NMR and ROESY spectra for compound **17** were recorded on a a Bruker DRX 600 spectrometer (600 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ=7.26, $^{13}CDCl_3$: δ=77.0). HR ESMS were performed on a Q-Star Applied Biosystem mass spectrometer. Infrared spectra were obtained at a resolution of 2.0 cm^{-1} with a Vector 22 Bruker spectrometer. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

4.2. Procedures for the synthesis of compounds 6–7, 9–14, described in paragraph 2.1

4.2.1. Compound 12. To a vigorously stirred mixture of (*S*)-carvone (**8**) (5.0 g, 33.3 mmol) and PtO_2 (0.013 g) in MeOH (40 mL), hydrogen was introduced, at room temperature. Hydrogenation was monitored by ^1H NMR. After disappearance of starting material, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo to give 5.1 g of crude carvotanacetone (**9**). Ozone was bubbled into a stirred solution of crude **9** in MeOH (63.5 mL) at −60 °C for 4 h. After

flushing off the excess ozone with N_2 for 30 min, to the reaction mixture was slowly added, at −60 °C, a mixture of Me_2S (4.40 mL), water (4.90 mL) and MeOH (14.8 mL) and the mixture was stirred overnight at room temperature. The reaction mixture, containing **10**, was then concentrated in vacuo to a half volume and to the residue was slowly added a solution of $NaIO_4$ (7.06 g, 33.3 mmol) in water (50 mL). The mixture was stirred vigorously for 4 h at room temperature. The white precipitate was filtered and repeatedly washed with ethyl acetate. The filtrate was extracted with ethyl acetate (3×100 mL) and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give crude **11**. To this was added MeOH (50 mL) and a catalytic amount of *p*-TsOH. The resultant mixture was stirred overnight at room temperature and then diluted with water and neutralized with a saturated solution of $NaHCO_3$. The mixture was concentrated in vacuo to remove the excess MeOH and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was flash chromatographed (10–30% diethyl ether in petroleum ether) to afford **12** (4.29 g, 59% over four steps) as an oil.

Compound **12**. R_f=0.65 (50% diethyl ether in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2958, 2831, 1738, 1440, 1370, 1126. $[\alpha]_D^{21}$=+2.1 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.84 (6H, d, *J*=6.9 Hz, $-CH(CH_3)_2$), 1.45 (1H, dddd, *J*=14.2, 8.4, 6.0 Hz, $-CHHCH(OCH_3)_2$), 1.62 (1H, dddd, *J*=14.2, 5.4, 5.4 Hz, $-CHHCH(OCH_3)_2$), 1.72 (1H, m, $-CH(CH_3)_2$), 1.93 (1H, m, $-CHCH(CH_3)_2$), 2.23 (1H, dd, *J*=15.3, 7.0 Hz, MeO_2CCHH-), 2.28 (1H, dd, *J*=15.3, 6.5 Hz, MeO_2CCHH-), 3.27 (3H, s, CH_3OCH-), 3.28 (3H, s, $CH_3'OCH-$), 3.64 (3H, s, $-COOCH_3$), 4.40 (1H, dd, *J*=6.0, 5.4 Hz, $(CH_3O)_2CH-$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.6, 18.8, 30.3, 33.7, 35.8, 36.7, 51.4, 52.4, 52.6, 103.4, 174.0. HR-ESMS: *m*/*z* 219.1587 (Calcd 219.1596 for $C_{11}H_{23}O_4$).

4.2.2. Compound 7. To a solution of the dimethyl acetal **12** (1.14 g, 5.2 mmol) in acetone and water (18.0 mL, 95:5), $Pd(MeCN)_2Cl_2$ (0.095 g, 0.366 mmol) was added at room temperature. The mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was dissolved in diethyl ether and filtered through a short pad of silica gel (particle size 0.040–0.063 mm). The filtrate was concentrated in vacuo to afford the desired aldehyde **7** (0.734 g, 82%) as a yellow oil, which was used in the next step without further purification.

Compound **7**. R_f=0.61 (50% diethyl ether in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2960, 2725, 1725, 1437, 1372, 1167, 1011. $[\alpha]_D^{25}$=−15.3 (*c* 1.4, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.86 (3H, d, *J*=6.9 Hz, $-CH(CH_3)$-CH_3), 0.87 (3H, d, *J*=6.9 Hz, $-CH(CH_3)CH_3$), 1.73 (1H, m, $-CH(CH_3)_2$), 2.23 (1H, m, $-CHCH(CH_3)_2$), 2.35–2.49 (4H, m, MeO_2CCH_2- and CH_2CHO overlapped), 3.68 (3H, s, $-COOCH_3$), 9.73 (1H, bs, $-CHO$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9 (×2), 30.7, 35.3, 35.9, 45.5, 51.6, 173.3, 202.0. HR-ESMS: *m*/*z* 173.1184 (Calcd 173.1178 for $C_9H_{17}O_3$).

4.2.3. Compound 13. To a solution of **2** (0.738 g, 1.39 mmol) and **7** (0.764 g, 4.43 mmol) in dry CH_2Cl_2 (24 mL), Me_2AlCl (1 M in hexane, 8.9 mL, 8.90 mmol) was added at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for 6 h and at −20 °C overnight and then quenched with a solution of MeOH/H_2O (20 mL, 1:1) at −78 °C. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were successively washed with 1% aqueous HCl, saturated aqueous $NaHCO_3$ and brine and then dried over $MgSO_4$. Removal of solvent in vacuo gave the crude reaction mixture which was purified by flash chromatography (10–40% diethyl ether in petroleum ether) to furnish pure **13** (0.853 g, 90%) as a white amorphous solid.

Compound **13**. R_f=0.56 (50% diethyl ether in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2958, 2930, 2854, 1735, 1471, 1428, 1373, 1242, 1111, 1087, 702. $[\alpha]_D^{23}$=−0.7 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.75 (3H, s, CH_3-18), 0.83 (3H, s, CH_3-19), 0.88 (6H, d, *J*=6.7 Hz, $(CH_3)_2CH-$), 1.05 (9H, s, $(CH_3)_3CSi-$), 1.14 (3H, d, *J*=6.8 Hz, CH_3-21), 1.79 (1H, dd, *J*=16.8, 11.2 Hz, H-15), 2.00–2.06 (2H, m, H′-15 and H-23 overlapped), 2.15 (1H, dd, *J*=17.7, 9.9 Hz, H-28), 2.25 (1H, m, H-20), 2.64 (1H, dd, *J*=17.7, 6.2 Hz, H′-28), 3.58 (1H, m, H-3), 4.23 (1H, ddd, *J*=11.0, 8.1, 2.1 Hz, H-22), 5.38 (1H, bs, H-16), 7.34–7.43 (6H, m, C_6H_5-), 7.68 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.3, 16.3, 18.2, 18.9, 19.1, 19.4, 20.9, 27.0 (×3), 28.6, 31.1, 31.2, 31.7, 31.8, 32.4, 33.6, 34.1, 34.8, 35.6, 36.8, 37.7, 38.3 (×2), 45.0, 47.4, 54.9, 57.1, 72.7, 83.4, 123.4, 127.4 (×4), 129.4 (×2), 134.8, 134.9, 135.7 (×4), 156.8, 172.4. HR-ESMS: *m*/*z* 681.4717 (Calcd 681.4703 for $C_{45}H_{65}O_3Si$).

4.2.4. Compound 14. To a solution of **13** (0.006 g, 0.009 mmol) in ethanol (1.5 mL), a catalytic amount of PtO_2 was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred overnight under hydrogen. It was then filtered through a pad of Celite® and concentrated in vacuo. Flash chromatography of the residue (30–40% diethyl ether in petroleum ether) gave pure **14** (0.006 g, quant.) as a white amorphous solid.

Compound **14**. R_f=0.72 (50% diethyl ether in petroleum ether). $[\alpha]_D^{25}$=+3.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.63 (3H, s, CH_3-18), 0.78 (3H, s, CH_3-19), 0.89 (3H, d, *J*=7.0 Hz, $-CH(CH_3)CH_3$), 0.90 (3H, d, *J*=7.0 Hz, $-CH(CH_3)CH_3$), 0.95 (3H, d, *J*=6.9 Hz, CH_3-21), 1.04 (9H, s, $(CH_3)_3CSi-$), 2.12 (1H, dd, *J*=17.8, 10.7 Hz, H-28), 2.64 (1H, ddd, *J*=17.8, 4.5, 1.5 Hz, H′-28), 3.58 (1H, m, H-3), 4.32 (1H, bd, H-22), 7.34–7.43 (6H, m, C_6H_5-), 7.67 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.9, 12.3, 12.6, 19.2 (×2), 19.3, 21.2, 24.0, 27.0 (×3), 27.6, 28.6, 30.2, 31.7, 31.9, 32.4, 34.1, 35.3, 35.5, 36.9, 38.0, 38.3, 39.7, 40.4, 42.4, 44.6, 51.6, 54.1, 56.1, 72.8, 82.5, 127.4 (×4), 129.3 (×2), 134.9 (×2), 135.7 (×4), 172.5. HR-ESMS: *m*/*z* 683.4867 (Calcd 683.4859 for $C_{45}H_{67}O_3Si$).

4.2.5. Compound 6. To a solution of **14** (0.044 g, 0.064 mmol) in dry CH_2Cl_2 (2.0 mL), DIBAL-H (1 M in THF, 0.193 mL, 0.193 mmol) was added at −78 °C. After 2 h at −78 °C, MeOH (0.5 mL) and H_2O (0.5 mL) were

sequentially added. After being warmed to room temperature, the mixture was diluted with diethyl ether (10 mL) and dried over $MgSO_4$. After stirring vigorously for 30 min, the mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo to give **6** (0.041 g, 93%) as a white amorphous solid.

Compound **6**. R_f=0.84 (50% diethyl ether in petroleum ether). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.58 (3H, s, CH_3-18), 0.73 (3H, s, CH_3-19), 0.81 (6H, d overlapped, J=7.0 Hz, $(CH_3)_2CH-$), 0.86 (3H, d, J=6.7 Hz, CH_3-21), 0.99 (9H, s, $(CH_3)_3CSi-$), 3.26 (0.5H, bd, J=10.8 Hz, H-22), 3.57 (1H, m, H-3), 3.84 (0.5H, bd, J=11.3 Hz, H′-22), 4.44 (0.5H, bt, J=7.5 Hz, H-29), 5.11 (0.5H, bs, H′-29), 5.68 (0.5H, d, J=3.8 Hz, $-OH$), 6.19 (0.5H, d, J=6.5 Hz, $-OH$), 7.42 (6H, m, C_6H_5-), 7.59 (4H, m, C_6H_5-). HR-ESMS: m/z 685.5027 (Calcd 685.5016 for $C_{45}H_{69}O_3Si$).

4.3. Procedures for the synthesis of compounds 15-17, 19-21, 23-26, 30, described in paragraph 2.2

4.3.1. Compounds 15 and 16. CrO_3 (0.882 g, 8.82 mmol) was finely ground with a mortar and pestle and dried in vacuo for 6 h. In an argon-purged flask, CrO_3 was suspended in dry CH_2Cl_2 (8.0 mL) and the resultant suspension was stirred for 15 min at room temperature. It was then cooled to −40 °C and the DMP (0.848 g, 8.82 mmol) was added in one portion. The dark red mixture was stirred at −40 °C for 30 min and then a solution of **13** (0.200 g, 0.294 mmol) in dry CH_2Cl_2 (15 mL) was added via cannula. The resultant thick, dark reaction mixture was allowed to warm to room temperature and stirred under argon overnight. NaOH solution (3 N, 9.5 mL) was subsequently added at 0 °C and the mixture was stirred for 45 min at room temperature. It was then diluted with diethyl ether (30 mL) and allowed to stir for additional 30 min. The organic phase was separated and the aqueous layer, containing a green precipitate, was washed with diethyl ether (3×30 mL). Filtration of the combined organic phases through a path of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded to a solution, which was concentrated in vacuo. The residue was flash chromatographed (40–70% diethyl ether in petroleum ether) to afford **15** (0.123 g, 60%) and **16** (0.023 g, 11%) as white amorphous solids.

Compound **15**. R_f=0.53 (60% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (3H, s, CH_3-19), 0.87 (6H, d, J=6.8 Hz, $(CH_3)_2CH-$), 0.98 (3H, s, CH_3-18), 1.05 (9H, s, $(CH_3)_3CSi-$), 1.25 (3H, d, J=6.8 Hz, CH_3-21), 1.95 (1H, bd, J=13.7 Hz, H-23), 2.18 (1H, dd, J=17.7, 9.9 Hz, H-28), 2.57 (1H, m, H-20), 2.63 (1H, m, H-7β), 2.70 (1H, dd, J=17.8, 6.5 Hz, H′-28), 3.58 (1H, m, H-3), 4.28 (1H, ddd, J=11.0, 8.1, 2.1 Hz, H-22), 5.70 (1H, s, H-16), 7.33–7.41 (6H, m, C_6H_5-), 7.67 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.3, 17.5, 18.8, 19.1, 19.3, 20.3, 23.5, 26.9 (×3), 28.1, 30.2, 30.8, 31.6, 32.3 (×2), 33.4, 35.7, 36.7, 37.4, 38.1 (×2), 38.7, 44.8, 47.1, 54.8, 63.7, 72.5, 81.9, 125.9, 127.4 (×4), 129.4 (×2), 134.6, 134.8, 135.7 (×4), 171.6, 183.1, 207.1. HR-ESMS: m/z 695.4499 (Calcd 695.4496 for $C_{45}H_{63}O_4Si$).

Compound **16**. R_f=0.28 (60% diethyl ether in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2960, 2931, 2856, 1728, 1471, 1427, 1242, 1217, 1111, 1087, 702. $[\alpha]_D^{23}$=+2.2 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (3H, s, CH_3-18), 0.79 (3H, s, CH_3-19), 0.88 (3H, d, J=6.7 Hz, $(CH_3)CH_3CH-$), 0.89 (3H, d, J=6.7 Hz, $CH_3(CH_3)CH-$), 1.03 (9H, s, $(CH_3)_3CSi-$), 1.11 (3H, d, J=6.9 Hz, CH_3-21), 1.92 (1H, bd, J=13.9 Hz, H-23), 2.15 (1H, dd, J=17.8, 9.7 Hz, H-28), 2.29 (1H, m, H-20), 2.64 (1H, dd, J=17.8, 6.5 Hz, H′-28), 3.36 (1H, s, H-16), 3.57 (1H, m, H-3), 3.97 (1H, ddd, J=11.0, 8.1, 2.1 Hz, H-22), 7.34–7.43 (6H, m, C_6H_5-), 7.67 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.2, 12.5, 15.1, 15.9, 18.9, 19.0, 19.2, 20.6, 26.9 (×3), 27.3, 28.4, 30.6, 31.5, 32.2, 32.3, 33.6, 34.8, 35.4, 36.7, 37.7, 38.1, 43.0, 44.2, 44.6, 54.4, 60.0, 65.7, 71.3, 72.5, 81.4, 127.3 (×4), 129.3 (×2), 134.7 (×2), 135.6 (×4), 171.9. HR-ESMS: m/z 697.4646 (Calcd 697.4652 for $C_{45}H_{65}O_4Si$).

4.3.2. Compound 17. *Compound* **15** (0.030 g, 0.043 mmol) was dissolved in 0.5 mL of a $CDCl_3$ solution and converted into **17** over 30 h at room temperature. The solution was concentrated in vacuo to give **17** (0.030 g, quant.) as a white amorphous solid.

Compound **17**. R_f=0.28 (60% diethyl ether in petroleum ether). $[\alpha]_D^{26}$=−0.9 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.74 (3H, s, CH_3-19), 0.86 (6H, d, J=6.7 Hz, $(CH_3)_2CH-$), 1.04 (9H, s, $(CH_3)_3CSi-$), 1.18 (3H, s, CH_3-18), 1.23 (3H, d, J=6.7 Hz, CH_3-21), 1.90 (1H, d, J=4.4 Hz, H-14), 2.15 (1H, dd, J=17.7, 9.9 Hz, H-28), 2.17 (1H, m, H-7α), 2.57 (1H, m, H-20), 2.65 (1H, dd, J=17.7, 6.4 Hz, H′-28), 3.53 (1H, m, H-3), 4.16 (1H, ddd, J=11.0, 8.1, 2.1 Hz, H-22), 5.98 (1H, s, H-16), 7.33–7.41 (6H, m, C_6H_5-), 7.65 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.9, 17.8, 18.9 (×2), 19.0, 19.3, 24.4, 26.9 (×3), 28.8, 30.8, 31.1, 32.3, 32.5, 33.6, 33.7 (×2), 36.2, 36.6, 37.6, 37.8, 38.1, 44.0, 44.5, 48.4, 57.0, 72.7, 82.6, 127.4 (×4), 129.4 (×2), 130.5, 134.6, 134.7, 135.7 (×4), 171.4, 185.4, 210.1. HR-ESMS: m/z 695.4511 (Calcd 695.4496 for $C_{45}H_{63}O_4Si$).

4.3.3. Compound 19. To a solution of **17** (0.054 g, 0.078 mmol) in ethyl acetate (4.5 mL), a catalytic amount of 5% Pt/C (0.007 g) was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred under hydrogen for 3 h. It was filtered through a pad of Celite® and concentrated in vacuo. Flash chromatography of the residue (40–50% diethyl ether in petroleum ether) gave **19** (0.054 g, quant.) as a white amorphous solid.

Compound **19**. R_f=0.55 (70% diethyl ether in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2959, 2932, 2857, 1731, 1471, 1427, 1386, 1249, 1216, 1110, 1078, 702. $[\alpha]_D^{23}$=−9.2 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$+20% C_6D_6, 600 MHz): δ 0.63 (3H, s, CH_3-19), 0.66 (3H, d, J=6.9 Hz, CH_3-21), 0.70 (3H, d, J=6.8 Hz, $(CH_3)CH_3CH-$), 0.71 (3H, d, J=6.8 Hz, $(CH_3)CH_3CH-$), 1.02 (3H, s, CH_3-18), 1.05 (9H, s, $(CH_3)_3CSi-$), 1.54 (1H, bs, H-14), 1.72 (1H, m, H-20), 1.80 (1H, m, H-17), 1.93–1.84 (2H, m, H-16 and H-28 overlapped), 2.09 (1H, dd, J=18.8, 8.8 Hz, H′-16), 2.37–2.45 (2H, m, H′-28 and H-7 overlapped), 3.55 (1H, m, H-3), 4.01 (1H, bd, J=11.7 Hz, H-22), 7.23–7.30 (6H, m, C_6H_5-), 7.65 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$,

100 MHz): δ 12.1, 12.2, 19.1 (×2), 19.3, 21.0, 23.1, 27.0 (×3), 28.7 (×2), 29.2 (×2), 31.4, 32.4, 33.3, 33.9, 35.4 (×2), 36.8, 38.0, 38.3, 39.5, 43.0, 43.8, 45.0, 47.7, 61.4, 72.7, 83.7, 127.4 (×4), 129.4 (×2), 134.7, 134.9, 135.7 (×4), 172.0, 217.8. HR-ESMS: *m/z* 697.4661 (Calcd 697.4652 for $C_{45}H_{65}O_4Si$).

4.3.4. Compound 20. To a solution of **15** (0.125 g, 0.180 mmol) in ethyl acetate (10 mL), previously neutralized with basic Al_2O_3, a catalytic amount of 5% Pt/C (0.010 g) was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred under hydrogen for 3 h. It was filtered through a pad of Celite® and concentrated in vacuo. Flash chromatography of the residue (40–50% diethyl ether in petroleum ether) gave **20** (0.119 g, 95%) as a white amorphous solid.

Compound **20**. R_f=0.45 (70% diethyl ether in petroleum ether). $[\alpha]_D^{23}$=+10.6 (*c* 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.72 (3H, s, CH_3-19), 0.79 (3H, s, CH_3-18), 0.906 (3H, d, *J*=6.8 Hz, (CH_3)CH_3CH–), 0.911 (3H, d, *J*=6.8 Hz, (CH_3)CH_3CH–), 1.03 (3H, d, *J*=6.8 Hz, CH_3-21), 1.04 (9H, s, (CH_3)$_3$CSi–), 1.76 (1H, dd, *J*=18.3, 9.7 Hz, H-16), 2.04 (1H, bd, *J*=12.5 Hz), 2.08–2.16 (2H, m, H-28 and H-17 overlapped), 2.48 (1H, dd, *J*=18.3, 8.8 Hz, H′-16), 2.58 (1H, bd, *J*=12.5 Hz), 2.66 (1H, dd, *J*=17.7, 6.2 Hz, H′-28), 3.57 (1H, m, H-3), 4.21 (1H, bd, *J*=11.1 Hz, H-22), 7.34–7.41 (6H, m, C_6H_5), 7.67 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.2, 12.8, 12.9, 19.2, 19.3, 20.7, 27.0 (×3), 28.2, 30.1, 30.3, 30.5, 31.6, 31.8, 32.3, 34.1, 35.4, 36.9, 38.0, 38.1, 39.7, 40.0, 41.1, 42.1, 44.5, 47.0, 53.7, 65.7, 72.6, 81.9, 127.4 (×4), 129.4 (×2), 134.7, 134.8, 135.7 (×4), 172.1, 214.8. HR-ESMS: *m/z* 697.4659 (Calcd 697.4652 for $C_{45}H_{65}O_4Si$).

4.4. C/D ring junction attempted isomerization of 20

To a solution of **20** (0.015 g, 0.021 mmol), in $CHCl_3$ (1.0 mL) was added 12 N HCl (0.050 mL) at room temperature. The reaction mixture was stirred at room temperature overnight then quenched with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo to give a residue containing the starting material **20** (0.015 g).

4.4.1. Compound 21. To a solution of **20** (0.078 g, 0.112 mmol) and hexamethyldisilazane (0.236 mL, 1.12 mmol) in dry CH_2Cl_2 (1.5 mL), lithium iodide (0.039 g, 0.291 mmol) and trimethylchlorosilane (TMS-Cl, 0.114 mL, 0.896 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 3 h and then quenched by addition of triethylamine (0.400 mL) and of a saturated solution of $NaHCO_3$ (0.600 mL) at 0 °C and diluted with diethyl ether. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo to give crude **21**, which was used in the next step without further purification.

Compound **21**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.14 (9H, s, (CH_3)$_3$Si–), 0.78 (3H, s, CH_3-18), 0.87 (3H, s, CH_3-19), 0.90–0.96 (9H, m, (CH_3)$_2$CH– and CH_3-21 overlapped), 1.05 (9H, s, (CH_3)$_3$CSi–), 2.67 (1H, dd, *J*=17.8, 6.2 Hz, H-28), 3.60 (1H, m, H-3), 4.24 (1H, bd, *J*=11.4 Hz, H-22), 7.34–7.43 (6H, m, C_6H_5–), 7.68 (4H, m, C_6H_5–). LR-ESMS: *m/z* 769.1 (Calcd 769.5 for $C_{48}H_{73}O_4Si_2$).

4.5. C/D ring junction attempted isomerization of 21

To a solution of crude **21** (0.025 g, 0.032 mmol) in THF (1.0 mL), TFA (0.150 mL) was slowly added at room temperature. The reaction mixture was stirred for 10 min at room temperature and then quenched with a saturated solution of $NaHCO_3$, concentrated in vacuo, to remove the excess THF, and extracted with diethyl ether. The organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. No trace of the *cis* C/D isomer was observed by ^{1}H NMR analysis of the crude residue, which was purified by flash chromatography (50–70% diethyl ether in petroleum ether) to give **20** (0.024 g).

4.5.1. Compounds 23 and 24. To a solution of **20** (0.058 g, 0.083 mmol) in dry CH_2Cl_2 (4.0 mL), DIBAL-H (1 M in CH_2Cl_2, 0.332 mL, 0.332 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, then quenched with a solution of MeOH/water (2.0 mL, 1:1) at −78 °C and stirred at room temperature for 20 min. Filtration through a pad of Celite® and concentration in vacuo afforded to a residue which was purified by flash chromatography (50ndash;90% diethyl ether in petroleum ether) to give **23** (0.028 g, 48%) and **24** (0.022 g, 38%) as white amorphous solids.

Compound **23**. R_f=0.60 (70% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (3H, s, CH_3-19), 0.85–0.97 (12H, m, CH_3-18, (CH_3)$_2$CH–, CH_3-21 overlapped), 1.04 (9H, s, (CH_3)$_3$CSi–), 3.39 (0.6H, bd, *J*=10.7 Hz, H-22), 3.58 (1H, m, H-3), 3.98 (0.4H, bd, *J*=11.3 Hz, H-22), 4.16 (1H, bt, *J*=6.0 Hz, H-15), 4.61 (0.6H, bd, *J*=8.7 Hz, H_{ax}-29), 5.34 (0.4H, bs, H_{eq}-29), 7.34–7.41 (6H, m, C_6H_5–), 7.67 (4H, m, C_6H_5–). HR-ESMS: *m/z* 701.4973 (Calcd 701.4965 for $C_{45}H_{69}O_4Si$).

Compound **24**. R_f=0.25 (70% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.64 (3H, s, CH_3-18), 0.79 (3H, s, CH_3-19), 0.84–0.90 (7.5H, m, (CH_3)$_2$CH– and CH_3-21 overlapped), 0.94 (1.5H, d, *J*=6.7 Hz, CH_3-21), 1.04 (9H, s, (CH_3)$_3$CSi–), 3.32 (0.5H, bd, *J*=10.6 Hz, H-22), 3.56 (1H, m, H-3), 3.89–3.95 (1.5H, m, H-15 and H-22 overlapped), 4.62 (0.5H, bd, *J*=8.7 Hz, H_{ax}-29), 5.36 (0.5H, bs, H_{eq}-29), 7.34–7.41 (6H, m, C_6H_5–), 7.66 (4H, m, C_6H_5–). HR-ESMS: *m/z* 701.4960 (Calcd 701.4965 for $C_{45}H_{69}O_4Si$).

4.5.2. Compound 26. To a solution of a mixture of **23** and **24** (0.028 g, 0.040 mmol) in CH_2Cl_2 (1.0 mL), HCl in MeOH (1 N, 2.0 mL) was added. The reaction mixture was stirred at room temperature for 1 h, quenched with Ag_2CO_3, stirred for 1 h, filtered and concentrated in vacuo to give **23** as a white amorphous solid which was used in the next step without further purification. To a solution of crude **23** in dry CH_2Cl_2 (2.0 mL), 4 Å molecular sieves (0.060 g) and PDC (0.030 g, 0.040 mmol) were added. The mixture was stirred at room temperature for 1 h, then diluted with diethyl ether (5.0 mL) and allowed to stir for additional

30 min. Filtration through a short pad of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution, which was concentrated in vacuo. The residue was flash chromatographed (30–70% diethyl ether in petroleum ether) to afford **26** (0.010 g, 55% on two steps) as a white amorphous solid.

Compound **26**. R_f=0.35 (50% diethyl ether in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.77 (3H, s, CH_3-19), 0.86 (3H, d, J=6.9 Hz, (CH_3)CH_3CH–), 0.87 (3H, d, J=6.9 Hz, (CH_3)CH_3CH–), 1.01 (3H, s, CH_3-18), 1.02 (1.8H, d, J=6.8 Hz, CH_3-21), 1.07 (1.2H, d, J=6.8 Hz, CH_3-21), 3.26 (0.4H, bd, J=10.8 Hz, H-22), 3.34 (1.8H, s, CH_3O), 3.47 (1.2H, s, CH_3O), 3.70 (0.6H, bd, J=11.2 Hz, H-22), 4.19 (0.4H, bd, J=8.7 Hz, H_{ax}-29), 4.76 (0.6H, bs, H_{eq}-29). HR-ESMS: m/z 473.3635 (Calcd 473.3631 for $C_{30}H_{49}O_4$).

4.6. C/D ring junction attempted isomerization of 26 with MeONa

To a solution of **26** (0.008 g, 0.017 mmol) in dry THF (0.500 mL), a solution of MeONa in dry methanol (1 M, 2.5 mL) was added. After 3 h at room temperature, the reaction mixture was refluxed for 2 days and then cooling at room temperature and diluted with diethyl ether. Filtration through a short pad of silica gel afforded a solution, which was concentrated in vacuo to give a residue containing starting material **26** (0.008 g).

4.7. C/D ring junction attempted isomerization of 26 with NaH

To a solution of **26** (0.008 g, 0.017 mmol) in dry THF (0.500 mL), was added NaH (0.010 mg, 0. 417 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and then refluxed for 3 days. It was then quenched by addition of water at 0 °C. The mixture was concentrated in vacuo to remove the excess THF and the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and evaporated in vacuo to give a complex mixture of unidentified compounds.

4.8. C/D ring junction attempted isomerization of 26 with NaOH

To a solution of **26** (0.008 g, 0.017 mmol) in 1:1 THF/EtOH (0.500 mL), was added 10% NaOH (0.100 mL) and the reaction mixture was stirred for 4 h at room temperature and then refluxed for 2 days. It was then quenched by addition of water at 0 °C. The mixture was concentrated in vacuo to remove the excess THF and the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and evaporated in vacuo to give a residue containing only the starting material **26** (0.008 g).

4.8.1. Compound 30. To a solution of **29** (0.300 g, 0.437 mmol) in dry CH_2Cl_2 (1.2 mL), DBU (0.120 g, 0.787 mmol) and TBSCl (0.105 g, 0.699 mmol) were added. The reaction mixture was stirred overnight at room temperature and then quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3×3.0 mL) and the combined organic phases were dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was flash-chromatographed (10% diethyl ether in petroleum ether) to afford **30** (0.289 g, 84%) as a white amorphous solid.

Compound **30**. R_f=0.71 (40% diethyl ether in petroleum ether). $[\alpha]_D^{20}$=+17.4 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.03 (6H, s, (CH_3)$_2$Si–), 0.73 (3H, s, CH_3-18), 0.88 (9H, s, (CH_3)$_3$CSi–), 0.96 (3H, s, CH_3-19), 0.99 (3H, d, J=6.8 Hz, CH_3-21), 1.04 (9H, s, (CH_3)$_3$CSi–), 1.87 (3H, s, OCCH_3), 1.96 (3H, s, OCCH_3), 3.39 (1H, dd, J=9.3, 9.3 Hz, H-22), 3.56 (2H, m, H-3 and H′-22 overlapped), 4.67 (1H, dd, J=9.4, 9.4 Hz, H-6 or H-7), 4.80 (1H, dd, J=11.2, 9.4 Hz, H-7 or H-6), 5.26 (1H, m, H-16), 7.34–7.43 (6H, m, C_6H_5–), 7.64 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3 (×2), 13.3, 15.9, 18.7, 19.1, 20.7, 21.0, 21.4, 25.6, 25.9 (×3), 26.9 (×3), 31.1, 32.0, 32.1, 34.3, 34.6, 36.0, 36.9, 38.0, 46.4, 47.9, 52.1, 54.7, 67.9, 72.0, 74.3, 77.7, 121.9, 127.4 (×4), 129.5 (×2), 134.5 (×2), 135.7 (×4), 156.8, 170.6, 170.8. HR-ESMS: m/z 801.4935 (Calcd 801.4946 for $C_{48}H_{73}O_6Si_2$).

4.9. C-15 attempted allylic oxidation with CrO_3-DMP

CrO_3 (0.080 g, 0.80 mmol) was finely ground with a mortar and pestle and dried in vacuo for 6 h. In an argon-purged flask, CrO_3 was suspended in dry CH_2Cl_2 (0.5 mL) and the resultant suspension was stirred for 15 min at room temperature. Then it was cooled to −40 °C and the DMP (0.077 g, 0.80 mmol) was added in one portion. The dark red mixture was stirred at −40 °C for 30 min and then a solution of **30** (0.032 g, 0.04 mmol) in dry CH_2Cl_2 (1.0 mL) was added via cannula. The resultant thick, dark reaction mixture was allowed to warm at room temperature and stirred under argon overnight. NaOH solution (3 N, 0.5 mL) was subsequently added at 0 °C and the mixture was stirred for 45 min at room temperature. Then it was diluted with diethyl ether (2.0 mL) and allowed to stir for additional 30 min. The organic phase was separated and the aqueous layer, containing a green precipitate, was washed with diethyl ether (3×2.0 mL). Filtration of the combined organic phases through a path of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution, which was concentrated in vacuo. The residue was flash chromatographed (10% diethyl ether in petroleum ether) to afford starting material **30** (0.080 g).

4.10. C-15 attempted allylic oxidation with SeO_2, *t*-BuOOH

To a suspension of SeO_2 (0.005 g, 0.050 mmol) in CH_2Cl_2, (0.800 mL) a solution of TBHP (5.5 M in nonane, 0.018 mL, 0.100 mmol) was added at 0 °C. After 0.5 h a solution of **30** (0.040 g, 0.050 mmol) in CH_2Cl_2 (0.800 mL) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with 10% NaOH aqueous solution and extracted with CH_2Cl_2, affording a complex mixture of unidentified compounds.

4.11. C-15 attempted allylic oxidation with CuI, *t*-BuOOH

To a solution of **30** (0.040 g, 0.050 mmol) in acetonitrile

(1.0 mL), copper iodide (1 mg) and TBHP (5.5 M in nonane, 0.054 mL, 0.300 mmol) were added. After one night, under magnetic stirring at 55 °C, the solution was poured into 10% sodium sulfite solution and extracted with diethyl ether. The residue contained only starting material **30** (0.038 g).

4.12. Computational details

Preliminary molecular mechanics/dynamics calculations on each of the compounds under examination were performed on Silicon Graphics Indigo2 using the CVFF force field[31] and the INSIGHT II/Discover package.[32] MD calculations (500 K, 50 ps) were executed in order to allow a full exploration of the conformational space. This led to the selection of the lowest energy minimum conformers. Subsequently, QM calculations were carried out using the Gaussian 98W program package; structures and energies of the considered species were optimized at AM1[33] and/or PM3[34] level.

Acknowledgements

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Synthesis of potentially anti-inflammatory IPL576,092-contignasterol and IPL576,092-manoalide hybrids

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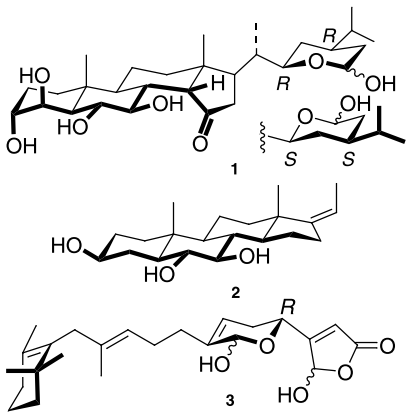
Abstract—The synthesis of two potentially anti-inflammatory steroidal hybrid compounds has been accomplished through a 16- and 17-step sequence, respectively, starting from commercially available androst-5-en-3β-ol-17-one. The synthetic strategies are based both on stereoselective side chains elaboration and high yielding functional group transformations.

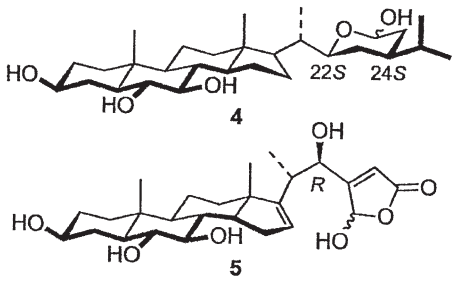
1. Introduction

Normal inflammation, a defense reaction caused by tissue damage or injury and characterized by redness, heat, swelling, and pain, is a highly regulated process. The inflammatory response, also involved in asthma and allergy, is induced by a localized release of histamine, leukotrienes, prostaglandins and cytokines.

With the recent discovery of the anti-inflammatory potential of contignasterol (**1**),[1] a polyhydroxysteroid isolated from the sponge *Petrosia contignata*, IPL576,092 (**2**),[2] a synthetic trihydroxypregnene, and manoalide (**3**), a marine sesterterpene isolated from the sponge *Luffariella variabilis*,[3] new perspectives have been opened in the treatment of inflammation-related pathological disorders.



Recently, a novel and promising approach in drug discovery, towards the development of new lead substances, has emerged. It consists in the combination of parts of structurally different naturally occurring bioactive products to yield hybrid structures that can, in principle, exceed the activities of their parent compounds.[4] From this perspective and as part of a broad program in the steroid area, we designed and synthesized the hybrid entities **4** and **5**, linking the IPL576,092 trihydroxylated tetracyclic nucleus to the contignasterol's (17*R*,20*S*,22*S*,24*S*)-lactol[5] and manoalide γ-hydroxybutenolide side chains, respectively. It is the preparation of these two new compounds that is reported here.



2. Results and discussion

Two important steps required to generate target compounds

Keywords: IPL576,092; Contignasterol; Manoalide; Steroids; Anti-inflammatory compounds.
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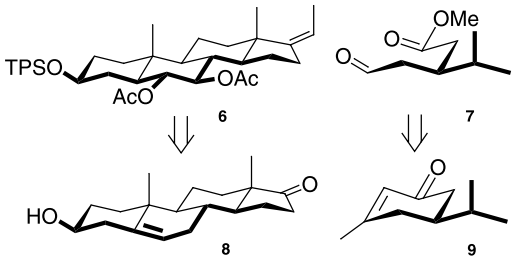
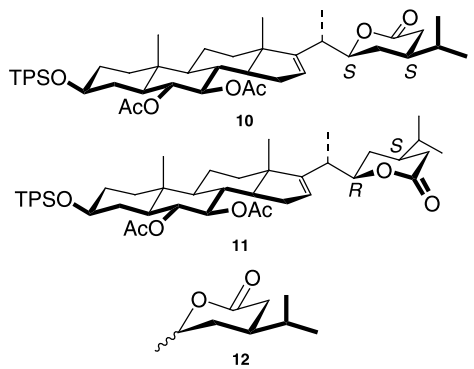
4 and **5** are: the synthesis of the fully protected common intermediate (*Z*)-6α,7β-(diacetoxy)-3β-[(*tert*-(butyldiphenysilyl)-oxy]-5α-pregn-17(20)-ene (**6**), and a highly reliable stereoselective method for the side chain precursor's introduction.

2.1. Synthesis of IPL576,092-contignasterol hybrid

Sterol **6** and preformed contignasterol's side chain intermediate **7** were conveniently prepared from commercially available androst-5-en-3β-ol-17-one (**8**), in 11 steps and 26% overall yield[6] and (*S*)-carvone (**9**), in five steps and 48% overall yield,[7] respectively.

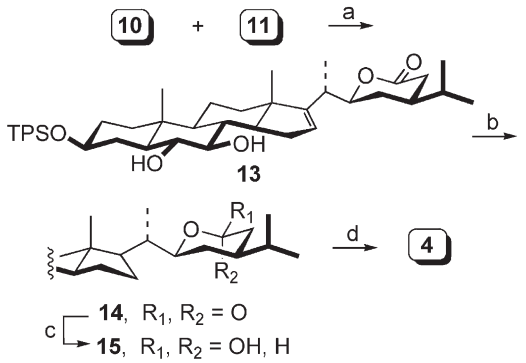


The two precursors **6** and **7** were linked through a stereochemically controlled Me_2AlCl-mediated carbonyl-ene reaction.[8] Although several ene reactions of linear aliphatic aldehydes have been reported,[8] we have encountered serious difficulties for the convergent coupling between **6** and **7**. The Lewis base character of the tetracyclic nucleus oxygenated substituents present in **6** and a probable 7β-acetoxy induced D ring unfavorable steric effect, could be the reasons of the low yields. The best results[9] were achieved using a two-fold excess of the Lewis acid relative to the aldehyde **7**[10] and afforded an inseparable mixture of diasteroimers **10** and **11**[11] (4:1 ratio in 66% overall yield, based on recovered starting material **6**). The excess of the Me_2AlCl acted as nucleophile, inducing the formation of the C-5 epimeric lactone **12**.



In order to suppress the formation of byproducts, we turned our attention to the non-alkylating $BF_3{\cdot}OEt_2$ Lewis acid.[12] Unfortunately, in this case, we observed the formation of a mixture of unidentified compounds, with no trace of the desired adduct **10**.

The next problem to be faced was transformation of precursor **10** to the requested target **4**. To this end the (20*S*,22*S*,24*S*)-Δ^{16}-lactone **10**, as a mixture with the (22*R*)-epimer **11**, was hydrolyzed and separated from its

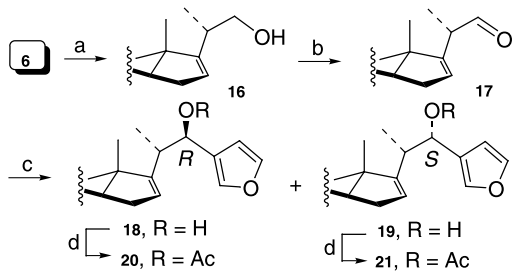


Scheme 1. (a) KOH, MeOH, 12 h, 70%; (b) H_2, Pt_2/C, AcOEt, 3 h, 90%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, quant.; (d) HF/pyridine, 0 °C, 3 days, 88%.

contaminant, to give pure **13** (Scheme 1). Highly stereoselective catalytic Δ^{16}-hydrogenation[7] and subsequent DIBAL-H mediated reduction, furnished the lactol **15**. Final HF-induced desilylation of the *tert*-(butyldiphenylsilyl) protecting group on C-3, provided the requested 3β,6α,7β-trihydroxy lactol **4** in good overall yield from intermediate **10**.[13]

2.2. Synthesis of IPL576,092-manoalide hybrid

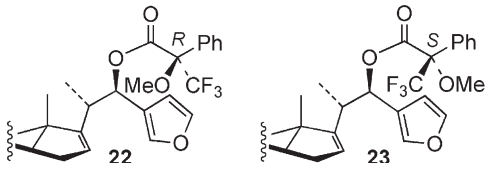
With the aim to combine IPL576,092 tetracyclic 3β,6α,7β-trihydroxylated nucleus with the γ-hydroxy butenolide manoalide[3]/luffariellolide[14] pharmacophore, we prepared the electrophilic aldehyde **17**, through a two-step sequence, from fully protected **6**, and exposed it to 3-furyllithium[15] (Scheme 2). The (*R*) stereochemistry of the major epimer **18** was assigned by comparison with the results observed for various alkyllithium or Grignard addition to this aldehyde, where the preferential formation of the Cram adduct is well documented.[16]



Scheme 2. (a) $BF_3{\cdot}OEt_2$, $(CH_2O)n$, CH_2Cl_2, −78 °C→−30 °C, 0.5 h, 90%;[6] (b) PDC, CH_2Cl_2, 2 h, 69%; (c) 3-bromofuran, *n*-BuLi, −78 °C, 15 min then **17**, −78 °C, 1 h, **18**: 57%, **19**: 28%; (d) Ac_2O, Py, 12 h, **20**: 95%, **21**: quant.

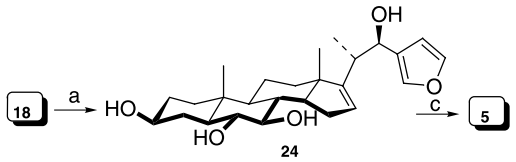
The stereochemical assignment was confirmed in two independent ways. It was empirically deduced by comparing the magnitude of the vicinal coupling of the $J_{H20-H22}$ in the acetylated derivatives **20** and **21**. It is known,[8] in fact, that the H-20/H-22 vicinal coupling constant should be smaller (~8 Hz) for the stereochemical arrangement present in **20** (20*S*,22*R*), and larger (~10 Hz) for that present in the epimer **21** (20*S*,22*S*). The observed $J_{H20-H22}$ coupling constants for **20** and **21** were 8.6 Hz and 10.7 Hz, respectively.

The (22*R*) configuration of **18** was also confirmed using the modified Mosher's esters method,[17] through comparison of the ^{1}H NMR spectra of α-methoxy-α-(trifluoromethyl)-phenylacetic (MTPA) derivatives **22** and **23**, easily achieved from (+)-(*S*)-MTPA-Cl and (−)-(*R*)-MTPA-Cl, respectively.[18]



Once ascertained the C-22 configuration of adducts **18** and **19**, we first desilylated at C-3 (Scheme 3) and then at C-6, C-7 deacetylated furyl alcohol **18**. Fully deprotected tetrol **24** was then submitted to a rose Bengal mediated photoxidation to give target γ-hydroxy butenolide **5**.[19]

The activity of hybrid **5** has been tested on human synovial $sPLA_2$-IIA, exerting a 63% of inhibition at 100 μM.[20] Additionally, this compound on lipopolysaccharide stimulated human monocytes was able to reduce nitric oxide and PGE_2 (two important mediators of the inflammatory process) at 10 μM (64 and 72%, respectively).[21]



Scheme 3. (a) (i) TBAF (1 M in THF), THF, 3 h; (ii) K_2CO_3, MeOH 12 h, 69% (two steps); (b) O_2/hν, rose Bengal, *i*-Pr_2EtN, CH_2Cl_2, −78 °C, 2 h, 40%.

3. Conclusions

In conclusion, we have reported the synthesis of two new IPL576,092-contignasterol and IPL576,092-manoalide analogs in 29 and 10% overall yields, respectively, starting from easily available (*Z*)-6α,7β-(diacetoxy)-3β-[(*tert*-(butyl-diphenysilyl)-oxy]-5α-pregn-17(20)-ene (**6**).

4. Experimental

4.1. General methods

The NMR spectra were recorded at room temperature on a Bruker DRX 400 spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz) or on Bruker DRX 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ=7.26, $^{13}CDCl_3$: δ=77.0, CD_2HOD: δ=3.31, $^{13}CD_3OD$: δ=49.0). Instruments used to obtain physical data and experimental conditions for the reactions and chromatography were the same as described in the preceding paper.[7]

4.2. Procedures for the synthesis of compounds 4, 10–15, described in paragraph 2.1

4.2.1. Compounds 10 and 11. To a solution of **6** (0.694 g, 1.05 mmol) and **7** (0.582 g, 3.38 mmol) in dry CH_2Cl_2 (15 mL), Me_2AlCl (1 M in hexane, 6.72 mL, 6.72 mmol) was added at −78 °C. The resulting mixture was warmed to −20 °C over 5 h and then stirred at −20 °C overnight. The reaction was quenched with MeOH/H_2O (18.0 mL, 1:1) at −78 °C. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic phases were successively washed with 1% aqueous HCl, saturated aqueous $NaHCO_3$, brine and then dried over Na_2SO_4. Removal of solvent in vacuo gave the crude containing **10** and **11** in a 4:1 ratio [^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ: 5.34 (0.8H, bs, H-16), 5.41 (0.2H, bs, H′-16)], which was purified by flash chromatography (20–80% diethyl ether in petroleum ether) to furnish a mixture of **10** and **11** (0.168 g, 20% overall yield, 66%, based on recovered starting material), of **6** (0.483 g, 70%) and **12** (variable amounts).

Compounds **10**–**11**. R_f=0.47 (30% ethyl acetate in petroleum ether). HR-ESMS: *m*/*z* 797.4817 (calcd 797.4813 for $C_{49}H_{69}O_7Si$).

Compound **12**. R_f=0.65 (30% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.84 (6H, d overlapped, *J*=7.0 Hz, −CH(C*H*$_3$)$_2$), 1.30 (1.5H, d, *J*=6.2 Hz, −CHC*H*$_3$), 1.31 (1.5H, d, *J*=6.2 Hz, −CHC*H*$_3$), 1.41–1.90 (4H, m, CHC*H*$_2$CH−, CH_2CHCH_2−, $(CH_3)_2CH$−, overlapped), 2.07 (0.5H, dd, *J*=17.7, 10.5 Hz, −C*H*HCOO), 2.17 (0.5H, dd, *J*=15.8, 11.1 Hz, −C*H*HCOO), 2.45 (0.5H, dd, *J*=15.8, 5.5 Hz, −CH*H*COO), 2.58 (0.5H, dd, *J*=17.7, 6.3 Hz, −CH*H*COO), 4.32 (0.5H, m, −*CH*OCO), 4.41 (0.5H, m, −*CH*OCO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ:19.0, 19.1, 19.2 (×2), 21.0, 21.8, 32.1 (×2), 32.6, 33.0, 33.4, 34.0, 35.0, 37.8, 73.8, 76.7, 172.0, 173.3. HR-ESMS: *m*/*z* 157.1237 (calcd 157.1229 for $C_9H_{17}O_2$).

4.2.2. Compound 13. *Compounds* **10** and **11** (0.115 g, 0.144 mmol) were dissolved in a 5% solution of KOH in MeOH (5.0 mL) and allowed to react overnight at room temperature. The reaction mixture was acidified with 2 M HCl to pH=1 at 0 °C. The solvents were concentrated in vacuo, to remove the excess MeOH, and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude, which was flash chromatographed (10–30% diethyl ether in chloroform) to give pure **13** (0.072 g, 70%) as a white amorphous solid and an inseparable mixture of **13** and its C-22 (*R*)-epimer (0.031 g).

Compound **13**. R_f=0.33 (30% diethyl ether in chloroform, double migration). IR ($CHCl_3$) ν_{max} (cm^{-1}) 3400, 2959, 2929, 2853, 1728, 1471, 1428, 1375, 1219, 1110, 1077, 772, 703. $[\alpha]_D$=+15.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (3H, s, CH_3-18), 0.872 (3H, s, CH_3-19), 0.873 (6H, d, *J*=6.3 Hz, (C*H*$_3$)$_2$CH−), 1.05 (9H, s, (C*H*$_3$)$_3$CSi−), 1.14 (3H, d, *J*=6.7 Hz, CH_3-21), 2.14 (1H, dd, *J*=17.7, 9.9 Hz, H-28), 2.64 (1H, dd, *J*=17.7, 6.6 Hz, H′-28), 3.04 (1H, dd, *J*=9.3, 8.9 Hz, H-6 or H-7), 3.21 (1H, dd, *J*=10.6, 8.9 Hz, H-7 or H-6), 3.56 (1H, m, H-3), 4.22 (1H, t-like, *J*=8.9 Hz, H-22), 7.34–7.43 (6H, m, C_6H_5−), 7.67 (4H, m, C_6H_5−). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.6, 16.1, 18.3, 18.9, 19.1, 19.3, 20.9, 27.0 (×3), 31.1, 31.3, 32.2, 32.4, 33.7, 34.0, 34.6, 35.9, 37.1, 37.7, 38.0, 39.7, 47.9,

48.0, 52.3, 56.0, 72.5, 74.8, 80.2, 83.5, 124.1, 127.4 (×2), 127.5 (×2), 129.4, 129.5, 134.6, 134.8, 135.8 (×4), 155.6, 172.3. HR-ESMS: *m*/*z* 713.4615 (calcd 713.4601 for $C_{45}H_{65}O_5Si$).

4.2.3. Compound 14. To a solution of **13** (0.042 g, 0.059 mmol) in ethyl acetate (3.0 mL), a catalytic amount of 5% Pt/C (0.008 g) was added. The flask was evacuated (50 Torr) and flushed three times with hydrogen. The reaction mixture was then vigorously stirred under hydrogen for 3 h at room temperature. It was filtered through a pad of Celite® and concentrated in vacuo to afford **14** (0.038 g, 90%) which was used in the next step without further purification.

Compound **14**. R_f=0.68 (50% ethyl acetate in petroleum ether). $[\alpha]_D$=+15.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, s, CH_3-18), 0.82 (3H, s, CH_3-19), 0.90 (6H, bd, *J*=6.3 Hz, $(CH_3)_2CH-$), 0.95 (3H, d, *J*=6.5 Hz, CH_3-21), 1.04 (9H, s, $(CH_3)_3CSi-$), 2.09 (1H, dd, *J*=17.7, 10.8 Hz, H-28), 2.64 (1H, dd, *J*=17.7, 6.6 Hz, H′-28), 3.01 (1H, dd, *J*=9.3, 8.9 Hz, H-6 or H-7), 3.18 (1H, dd, *J*=10.6, 8.9 Hz, H-7 or H-6), 3.54 (1H, m, H-3), 4.33 (1H, bd, *J*=11.2 Hz, H-22), 7.34–7.43 (6H, m, C_6H_5-), 7.67 (4H, m, C_6H_5-). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.0, 12.6, 13.6, 19.1, 19.2, 19.3, 21.2, 26.5, 27.0 (×3), 28.0, 30.2, 31.2, 32.2, 32.4, 34.1, 35.5, 37.2, 38.0, 39.5, 40.3, 40.8, 43.2, 47.5, 50.6, 51.8, 55.5, 72.5, 74.8, 80.5, 82.5, 127.4 (×4), 129.4 (×2), 134.5, 134.8, 135.7 (×4), 172.7. HR-ESMS: *m*/*z* 715.4747 (calcd 715.4758 for $C_{45}H_{67}O_5Si$).

4.2.4. Compound 15. To a solution of **14** (0.033 g, 0.046 mmol) in dry CH_2Cl_2 (2.0 mL), DIBAL-H (1 M in CH_2Cl_2, 0.230 mL, 0.230 mmol) was added at −78 °C. The reaction mixture was stirred at −78 °C for 90 min, then quenched with MeOH/H_2O (1.0 mL, 1:1) at −78 °C and stirred at room temperature for 20 min. Filtration through a pad of Celite® and concentration in vacuo afforded to a residue which was purified by flash chromatography (30–50% ethyl acetate in petroleum ether) to give **15** (0.033 g, quant.) as a white amorphous solid.

Compound **15**. R_f=0.66 (50% ethyl acetate in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.64 (3H, s, CH_3-18), 0.83 (3H, s, CH_3-19), 0.86–0.96 (9H, m, $(CH_3)_2CH-$, CH_3-21 overlapped), 1.05 (9H, s, $(CH_3)_3CSi-$), 3.01 (1H, dd, *J*=9.3, 8.9 Hz, H-6 or H-7), 3.18 (1H, dd, *J*=10.6, 8.9 Hz, H-7 or H-6), 3.41 (0.6H, bd, *J*=10.3 Hz, H-22), 3.54 (1H, m, H-3), 3.99 (0.4H, bd, *J*=11.1 Hz, H-22), 4.62 (0.6H, bd, *J*=8.9 Hz, H_{ax}-29), 5.34 (0.4H, bs, H_{eq}-29), 7.34–7.41 (6H, m, C_6H_5-), 7.67 (4H, m, C_6H_5-). HR-ESMS: *m*/*z* 717.4917 (calcd 717.4914 for $C_{45}H_{69}O_5Si$).

4.2.5. Compound 4. To a solution of **15** (0.044 g, 0.061 mmol) in dry pyridine (0.600 mL), 70% HF in pyridine (0.073 mL) was added at 0 °C. The reaction mixture was stirred for 3 days at 0 °C and then diluted with $CHCl_3$. The solvents were removed under a N_2 stream and the residue was flash-chromatographed (5–20% methanol in a 0.1% solution of triethylamine in dichloromethane) to afford **4** (0.026 g, 88%) as a white amorphous solid.

Compound **4**. R_f=0.17 (10% methanol in dichloromethane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, bs, CH_3-18), 0.83–0.96 (6H, m, CH_3-19, CH_3-21 and $(CH_3)_2CH-$ overlapped), 3.03 (1H, m, H-6 or H-7), 3.18 (1H, m, H-7 or H-6), 3.40 (0.5H, bd, *J*=8.3 Hz, H-22), 3.60 (1H, m, H-3), 4.01 (0.5H, bd, *J*=10 Hz, H_{ax}-29), 4.63 (0.5H, bd, *J*=8.0 Hz, H-22), 5.31 (0.5H, bs, H_{eq}-29). HR-ESMS: *m*/*z* 479.3749 (calcd 479.3736 for $C_{29}H_{51}O_5$).

4.3. Procedures for the synthesis of compounds 5, 17–24, described in paragraph 2.2

4.3.1. Compound 17. To a solution of **16**[6] (0.202 g, 0.29 mmol) in dry CH_2Cl_2 (10 mL), 4 Å molecular sieves (0.20 g) and PDC (0.22 g, 0.59 mmol) were added. The mixture was stirred at room temperature for 3 h, then diluted with diethyl ether (10 mL) and allowed to stir for additional 45 min. Filtration through pad of silica gel (particle size 0.063–0.200 mm) and $CaSO_4$ (10% in weight) afforded a solution which was concentrated in vacuo. The residue was flash-chromatographed (10–20% ethyl acetate in petroleum ether) to afford **17** (0.140 g, 69%) as a pale yellow oil.

Compound **17**. R_f=0.44 (20% ethyl acetate in petroleum ether). $[\alpha]_D$=+17.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.75 (3H, s, CH_3-18), 0.95 (3H, s, CH_3-19), 1.02 (9H, s, $(CH_3)_3CSi-$), 1.15 (3H, d, *J*=6.7 Hz, CH_3-21), 1.87 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CO), 2.97 (1H, bq, *J*=5.4 Hz, H-20), 3.54 (1H, m, H-3), 4.68 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.77 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.42 (1H, bs, H-16), 7.37 (6H, m, C_6H_5-), 7.63 (4H, m, C_6H_5-), 9.39 (1H, d, *J*=2.3 Hz, H-22). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.0, 14.0, 15.5, 18.7, 20.3, 20.5, 21.1, 26.6 (×3), 30.7, 31.8 (×2), 31.9, 33.6, 35.6, 36.5, 37.6, 45.4, 46.0, 51.6, 54.3, 71.6, 73.8, 77.2, 126.9, 127.1 (×4), 129.2 (×2), 134.1, 134.2, 135.4 (×4), 150.3, 170.3, 170.4, 200.5. HR-ESMS: *m*/*z* 685.3931 (calcd 685.3924 for $C_{42}H_{57}O_6Si$).

4.3.2. Compounds 18 and 19. To a solution of 3-bromofuran (0.065 mL, 0.72 mmol) in dry THF (2.5 mL), *n*-BuLi (1.6 M in hexane, 0.32 mL, 0.51 mmol) was added at −78 °C. After being stirred for 30 min, to the resulting mixture was added a solution of **17** (0.071 g, 0.10 mmol) in dry THF (2.5 mL) and the mixture was stirred for 30 min at −78 °C. The mixture was neutralized with saturated aqueous NH_4Cl, concentrated in vacuo, to remove the excess THF, and extracted with diethyl ether. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was flash-chromatographed (15–40% of ethyl ether in petroleum ether) to give **18** (0.036 g, 57%) and **19** (0.018 g, 28%) as oils.

Compound **18**. R_f=0.50 (30% ethyl acetate in petroleum ether). IR ($CHCl_3$) ν_{max} (cm^{-1}) 2936, 2856, 1743, 1376, 1251, 1110, 1081, 1029, 703. $[\alpha]_D$=+8.4 (*c* 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.65 (3H, s, CH_3-18), 0.94 (3H, s, CH_3-19), 1.01 (3H, d, *J*=6.7 Hz, CH_3-21), 1.02 (9H, s, $(CH_3)_3CSi-$), 1.87 (3H, s, CH_3CO), 1.96 (3H, s, CH_3CO), 2.40 (1H, m, H-20), 3.52 (1H, m, H-3), 4.66 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.74 (1H, d, *J*=5.6 Hz, H-22), 4.78 (1H, dd, *J*=9.9, 9.4 Hz, H-6 or H-7), 5.46 (1H, bs, H-16), 6.31 (1H, bs, H-4′), 7.38, (8H, m, C_6H_5-, H-2′ and

H-5′ overlapped), 7.62 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 15.5, 15.9, 19.1, 20.7, 20.9, 21.4, 26.9 (×3), 31.1, 32.0, 32.1, 34.2, 36.0, 36.8, 37.8, 38.8, 46.4, 47.7, 52.0, 55.2, 69.3, 72.0, 74.3, 77.6, 108.7, 124.7, 127.5 (×4), 127.8, 129.5 (×2), 134.5, 134.6, 135.7 (×4), 139.4, 142.8, 156.0, 170.6, 170.8. HR-ESMS: *m/z* 753.4179 (calcd 753.4187 for $C_{46}H_{61}O_7Si$).

Compound **19**. R_f=0.35 (30% ethyl acetate in petroleum ether). $[\alpha]_D$=+40.7 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.37 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.15 (3H, d, *J*=6.7 Hz, CH_3-21), 1.86 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.74 (1H, m, H-20), 3.51 (1H, m, H-3), 4.65 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (2H, m, H-7 or H-6 and H-22 overlapped), 5.41 (1H, bs, H-16), 6.31 (1H, bs, H-4′), 7.27–7.40 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.62 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 15.0, 18.9, 19.0, 20.7, 20.9, 21.4, 26.9 (×3), 31.1, 32.0, 32.1, 34.2, 35.9, 36.8, 36.9, 37.0, 37.8, 46.3, 48.0, 52.0, 54.6, 68.9, 72.0, 74.2, 77.5, 113.7, 123.6, 127.5 (×4), 129.5 (×2), 134.4, 134.5, 135.7 (×4), 141.5, 152.0, 155.0, 170.6, 170.8. HR-ESMS: *m/z* 753.4191 (calcd 753.4187 for $C_{46}H_{61}O_7Si$).

4.3.3. Compounds 20 and 21. To a solution of **18** (or **19**) (0.010 g, 0.013 mmol) in dry pyridine (0.100 mL), Ac_2O (0.040 mL) was added. The resulting mixture was stirred overnight, concentrated under a N_2 stream and flash-chromatographed (10–20% of ethyl acetate in petroleum ether) to give **20** (0.010 g, 95%) or **21** (0.011 g, quant.) as oils.

Compound **20**. R_f=0.59 (50% diethyl ether in petroleum ether). $[\alpha]_D$=+4.8 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.45 (3H, s, CH_3-18), 0.92 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.06 (3H, d, *J*=6.7 Hz, CH_3-21), 1.86 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.47 (1H, m, H-20), 3.51 (1H, m, H-3), 4.64 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.76 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.33 (1H, bs, H-16), 5.78 (1H, d, *J*=8.6 Hz, H-22), 6.27 (1H, bs, H-4′), 7.27–7.40 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.62 (4H, m, –C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 15.3, 15.9, 19.1, 20.7, 20.9, 21.2, 27.0 (×3), 29.7, 31.2 (×2), 32.2 (×2), 34.4, 36.0, 36.9, 37.3, 37.9, 46.4, 48.0, 52.1, 54.8, 71.7, 72.0, 74.3, 109.2, 124.1, 124.5, 127.5 (×4), 129.5 (×2), 134.7 (×2), 135.7 (×4), 140.5, 142.6, 154.6, 170.3, 170.6, 170.8. HR-ESMS: *m/z* 795.4285 (calcd 795.4292 for $C_{48}H_{63}O_8Si$).

Compound **21**. R_f=0.69 (30% ethyl acetate in petroleum ether). $[\alpha]_D$=+34.8 (*c*=0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.30 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.08 (3H, d, *J*=6.7 Hz, CH_3-21), 1.85 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 2.79 (1H, m, H-20), 3.50 (1H, m, H-3), 4.63 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.47 (1H, bs, H-16), 5.89 (1H, d, *J*=10.7 Hz, H-22), 6.31 (1H, bs, H-4′), 7.34–7.41 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.62 (4H, m, C_6H_5–). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.3, 14.9, 19.1, 19.4, 20.7, 20.8, 20.9, 21.4, 26.9 (×3), 29.8, 32.1 (×2), 34.2, 34.8, 35.9, 36.8, 37.8, 46.4, 48.1, 52.0, 54.4, 69.8, 72.0, 74.2, 77.5, 113.9, 124.0 (×2), 127.5 (×4), 129.5 (×2), 134.6 (×2), 135.7 (×4), 141.9, 149.0, 153.7, 170.0, 170.6, 170.8. HR-ESMS: *m/z* 795.4281 (calcd 795.4292 for $C_{48}H_{63}O_8Si$).

4.3.4. Compounds 22 and 23. To a solution of **18** (0.010 g, 0.013 mmol) in dry pyridine (0.150 mL), (*S*)-MTPA-Cl (or (*R*)-MTPA-Cl 0.007 mL) was added at 0 °C. The resulting mixture was stirred 1 h, concentrated under a N_2 stream and flash-chromatographed (30% of diethyl ether in petroleum ether) to give **22** (or **23**) in quantitative yield.

Compound **22**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.40 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 0.93 (3H, d, *J*=6.7 Hz, CH_3-21), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.86 (3H, s, CH_3CO), 1.94 (3H, s, CH_3CO), 2.53 (1H, m, H-20), 3.40 (4H, m, H-3 and CH_3O– overlapped), 4.62 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.28 (1H, bs, H-16), 5.95 (1H, d, *J*=9.6 Hz, H-22), 6.31 (1H, bs, H-4′), 7.31–7.41 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.63 (4H, m, C_6H_5–). LR-ESMS: *m/z* 969.9 (calcd 969.5 for $C_{56}H_{68}F_3O_9Si$).

Compound **23**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.40 (3H, s, CH_3-18), 0.91 (3H, s, CH_3-19), 1.02 (9H, s, (CH_3)$_3$CSi–), 1.09 (3H, d, *J*=6.7 Hz, CH_3-21), 1.85 (3H, s, CH_3CO), 1.95 (3H, s, CH_3CO), 2.53 (1H, m, H-20), 3.49 (4H, m, H-3 and CH_3O– overlapped), 4.63 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 4.75 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6), 5.33 (1H, bs, H-16), 5.90 (1H, d, *J*=8.8 Hz, H-22), 6.14 (1H, bs, H-4′), 7.31–7.41 (8H, m, C_6H_5–, H-2′ and H-5′ overlapped), 7.63 (4H, m, C_6H_5–). LR-ESMS: *m/z* 969.1 (calcd 969.5 for $C_{56}H_{68}F_3O_9Si$).

4.3.5. Compound 24. To a solution of **18** (0.170 g, 0.23 mmol) in dry THF (3.0 mL), *tetra*-butylammonium fluoride (TBAF, 1 M in THF, 0.92 mL, 0.92 mmol) was added. The mixture was stirred at room temperature for 3 h, then diluted with H_2O, concentrated in vacuo, to remove the excess THF, and extracted with diethyl ether. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. To a solution of the residue in MeOH (2.0 mL), K_2CO_3 (0.010 g, 0.072 mmol) was added. The mixture was stirred at reflux overnight and then quenched with $CHCl_3$ (3.0 mL). Solvents were concentrated in vacuo to the half of their volume. The procedure ($CHCl_3$ addition and concentration) was repeated several times to precipitate the carbonate. The solution was then filtrate through a pad of Celite®, concentrated in vacuo and the residue was flash-chromatographed (2–30% MeOH in CH_2Cl_2) to give **24** (0.066 g; 69% for two steps) as a white amorphous solid.

Compound **24**. R_f=0.74 (25% methanol in chloroform). $[\alpha]_D$=+32.6 (*c* 0.8, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.70 (3H, s, CH_3-18), 0.89 (3H, s, CH_3-19), 1.04 (9H, s, (CH_3)$_3$CSi–), 1.06 (3H, d, *J*=6.7 Hz, CH_3-21), 2.46 (1H, m, H-20), 3.13 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 3.28 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6) 3.58 (1H, m, H-3), 4.79 (1H, d, *J*=5.6 Hz, H-22), 5.60 (1H, bs, H-16), 6.33 (1H, bs, H-4′), 7.35 (2H, bs, H-2′ and H-5′). ^{13}C NMR (CD_3OD, 100 MHz) δ: 14.0, 15.9, 18.5, 18.8, 22.4, 31.9, 33.3, 35.1, 36.2, 37.0, 38.5, 40.6, 41.2, 49.8, 54.0, 58.1, 71.0, 71.9, 75.9, 81.1, 110.4, 125.3, 130.3, 141.0, 143.7, 157.6. HR-ESMS: *m/z* 431.2787 (calcd 431.2797 for $C_{26}H_{39}O_5$).

4.3.6. Compound 5. To a solution of **24** (0.020 g, 0.048 mmol) in dry CH_2Cl_2 (2.0 mL) and THF (1.0 mL), diisopropylethylamine (0.85 mL) and rose Bengal (0.001 g) were added. The mixture was irradiated at −78 °C with a 200-W tungsten incandescent lamp for 2 h. The reaction mixture was allowed to warm to 20 °C and concentrated in vacuo. The crude residue was purified by HPLC (Vydac C_{18} analytical column; 10–95% of CH_3CN and 0.1% TFA in H_2O and 0.1% TFA) to give **5** in (0.009 g, 40%) as a white amorphous solid.

Compound **5**. R_f=0.60 (25% methanol in chloroform). $[\alpha]_D$=+46.9 (*c* 0.8, CH_3OH). ^1H NMR (CD_3OD, 400 MHz) δ: 0.89 (3H, s, CH_3-18), 0.94 (3H, s, CH_3-19), 1.06 (3H, d, *J*=6.7 Hz, CH_3-21), 2.49 (1H, m, H-20), 3.04 (1H, dd, *J*=11.0, 9.4 Hz, H-6 or H-7), 3.18 (1H, dd, *J*=9.9, 9.4 Hz, H-7 or H-6) 3.51 (1H, m, H-3), 4.60 (1H, bd, *J*=3.8 Hz, H-22), 5.69 (1H, bs, H-16), 6.12 (1H, bs, C=C*H*CO), 6.40 (1H, bs, HOC*H*O–). HR-ESMS: *m/z* 463.2690 (calcd 463.2696 for $C_{26}H_{39}O_7$).

Acknowledgements

This work has been supported by the MIUR ('Sostanze naturali ed analoghi sintetici con attività antitumorale') and by the Università degli Studi di Salerno. LEO Pharma staff of Denmark and Prof. Miguel Payá (Departamento de Farmacologia, Facultad de Farmacia, Universidad de Valencia, Spain) are gratefully acknowledged for the in vitro anti-inflammatory tests.

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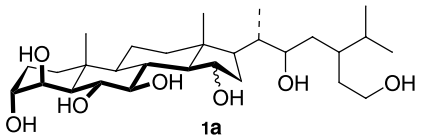
5. We have recently reported the synthesis of a series of model compounds containing the four possible C-22/C-24 stereoisomers Izzo, I.; Pironti, V.; Della Monica, C.; Sodano, G.; De Riccardis, F. *Tetrahedron Lett.* **2001**, *42*, 8977–8980, and proposed a (22*S*,24*S*) configuration for the natural product. After ten years from its first isolation, Andersen completed contignasterol's structural elucidation and assigned as (22*R*, 24*R*) the configurations of the side chain's stereogenic centres Yang, L.; Andersen, R. J. *J. Nat. Prod.* **2002**, *65*, 1924–1926, Considering still in doubt the assignment of the C-22/C-24 stereogenic centres, we decided to synthesize a (17*R*,20*S*,22*S*, 24*S*)-side chain. It must be stressed that side chain seems to be quite important for contingasterol's activity. Infact, contignasterol's reduction product **1a** did not inhibit histamine relase from rat mast cells (Ref. 1b), suggesting that either the 15-keto group and/or the hemiacetal is necessary for the inhibition of histamine relase. The authors represent **1a** as having the *trans* C/D ring junction, yet it is doubtful that the reduction conditions would cause epimerization of the 14β-hydrogen



1a

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10. It is known that a lower ratio between Lewis acid and aldehyde induces an Oppenauer-type oxidation of the secondary alcohol present in the adduct (see Scheme II of Ref. 8).
11. The C-22 stereochemistries were assigned on strenght of comparative analysis with our previous results. See: Izzo, I.; Pironti, V.; Della Monica, C.; Sodano, G.; De Riccardis, F. *Tetrahedron Lett.* **2001**, *42*, 8977–8980.
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19. Spectroscopic data of the γ-hydroxy butenolide mojety are consistent with those reported on literature. See: Kernan, M. R.; Faulkner, D. J. *J. Am. Chem. Soc.* **1988**, *53*, 2773–2776.
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A selective one-step synthesis of tris *N*-alkylated cyclens☆

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Abstract—A general one-step synthesis for tris *N*-alkylated cyclens with good yield and unprecedented selectivity is presented. Tris and 1,4-bis *N*-alkylated cyclens, as the only two major products are isolated. Furthermore, according to the single crystal X-ray structures of tris and 1,4-bis *N*-alkylated cyclen **1** and **1a**, one nitrogen atom on the cyclen ring can be protonated under this reaction condition, which prevents its further alkylation, and gives rise to the regioselectivity ultimately.

1. Introduction

Ln^{3+} complexes that are based on multidentate 1,4,7,10-tetraazacyclododecane (cyclen) show high thermodynamic and kinetic stabilities in aqueous solution, and have been widely used as Magnetic Resonance Imaging (MRI) contrast agents (CAs),[1] radio-pharmaceuticals,[2] luminescence probes or switches,[3] and RNA cleavers,[4] etc. For example, the octacoordinate Gd^{3+} complex, [Gd-DOTA $(H_2O)]^-$ (Dotarem™)[5], is one of the most widely used contrast agents in clinics (Fig. 1). Compared to octacoordinate Ln^{3+} complexes, there has been a growing interest in macrocyclic heptacoordinate Ln^{3+} complexes, especially the tris *N*-carboxymethyl-1,4,7,10-tetraazacyclodecane (DO3A) derivatives. Firstly, in DO3A derivatives, with the exception of three pendant chelating moieties that are utilized for strong lanthanide chelation, the remaining NH can be derivatized freely to improve the organ/tissue selectivity,[6] fine tune the intramolecular energy transfer,[7] or increase the enzymatic responding ability.[8] Secondly, a maximum of two coordinated sites is left for the binding of water molecules in these heptadentate Ln^{3+} complexes, which makes the relaxivity of Gd^{3+} complexes increase effectively because the inner-sphere proton relaxivity is linearly proportional to the number of directly coordinated water molecules.[9] Lastly, three chelating moieties with negative charges such as carboxylate can neutralize the Ln^{3+}; the resulting neutral complexes with low osmolality can effectively reduce the pain and tissue sloughing during the injection process.

Several selective functionalizations of cyclen to prepare DO3A derivatives have been reported. Before the alkylation is performed, three amines in the cyclen can be temporarily protected by the protective groups such as *tert*-butyloxycarbonyl,[10] tosyl[11], formyl,[12] trifluoroacetyl,[13] or by the sterically hindered reagents including phosphoryl species,[14] glyoxal aminal,[15] and metal carbonyls $M(CO)_6$ (M=Cr, Mo,

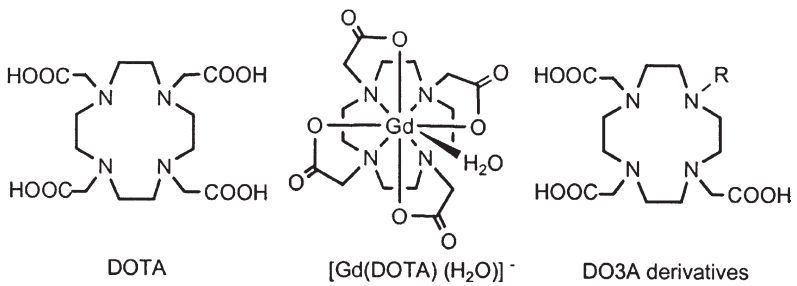

Figure 1. Structures of DOTA, Gd-DOTA and DO3A derivatives.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.04.086

Keywords: One-step synthesis; Alkylation; Cyclen.
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W)[16] from the inside of the tetraazamacrocycles in a stoichiometric ratio. Therefore, all the procedures above involve a protection, alkylation, deprotection, and alkylation sequence. Even in the recent work of Welch, tris *N*-alkylated cyclens were prepared from cyclen through four such steps.[17] In principle, the most efficient method to prepare tris *N*-alkylated cyclens is selective alkylation of three NH on the cycle with chelating agents (such as acetic acid, amides, etc.) directly, after which selected functional groups can be introduced to the remaining amine. Even though several synthetic procedures for tris *N*-alkylated cyclens through one-step alkylation were reported,[18] unfortunately they are not always general, and the yields of tris *N*-alkylated cyclens fluctuate between 20 and 50% due to the formation of tetra *N*-alkylated byproducts. Hence, the challenge still remains in exploiting a straightforward procedure to prepare tris *N*-alkylated cyclens with high selectivity.

2. Results and discussion

In our previous studies, we described direct methods for the preparations of mono *N*-alkylated cyclen,[19] and 1,4-bis *N*-alkylated cyclen.[20] 1,4-Bis(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane **1a** as the only bis *N*-alkylated isomer was isolated in good yield by the treatment of 2.0 equiv. of *tert*-butyl bromoacetate with cyclen in chloroform. As reported, 6–10% of tris (*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane **1** was developed as a side-product in this circumstance.[20] To promote the yield of this important precursor of DO3A chelate, an additional electrophile was added under similar reaction conditions. The yield of **1** increased dramatically, and an optimal value of 77% was achieved in the presence of 3.5 equiv. of electrophile, much higher than that previously reported.[18] Surprisingly, apart from about 20% of 1,4-bis *N*-alkylated product **1a**, no other alkylated products were isolated.

To clarify the solvent and auxiliary base's effect on the regioselectivity, this reaction was also performed in different solvents with various auxiliary bases (Table 1). The $CHCl_3/(Et)_3N$ system afforded the most satisfactory result (entry 4, Table 1). The effect of solvents on the yield and selectivity is obvious. Weakly polar and aprotic solvents like CH_3Cl and CH_2Cl_2 are preferable to polar, aprotic solvents such as DMF, CH_3CN, and polar, protic solvents such as CH_3OH, which lead to substantial losses in yield and selectivity[22] (entries 6–8, Table 1). Auxiliary bases also play an important role in determining the regioselectivity (entries 1–4, Table 1). A yield of only 35% of tris *N*-alkylated cyclen **1** was achieved if $(Et)_3N$ was replaced by K_2CO_3. Furthermore, in the presence of K_2CO_3, nearly all cyclen was tetra *N*-alkylated in the presence of 8.0 equiv. of electrophile.

To further investigate the regioselectivity and distribution of different *N*-alkylated products in the $CHCl_3/(Et)_3N$ system, a series of experiments was conducted in the presence of *tert*-butyl bromoacetate from 2.0 to 8.0 equiv. (Fig. 2). 1,4-Bis *N*-alkylated cyclen **1a** and tris *N*-alkylated cyclen **1** were the only two products that were isolated in the whole reaction process. The yield of **1** increased gradually and reached approximately 77% in the presence of about 3.5 equiv. of alkylating agent. At the same time, the yield of **1a** decreased from 81 to 20%. Interestingly, the regioselectivity was kept nearly constant, and no tetra *N*-alkylated cyclen was found even in a large excess of 8.0 equiv. of electrophile.

Table 1. Effect of solvent and auxiliary base on the yield and regioselectivity

Entry	Cond.[a]	Base	Yield (%)[b]			
			Tris	Bis	Tetra	r^c
1	$CHCl_3$	Free	51	40	n.d.[d]	>99
2	$CHCl_3$	Pyridine[e]	63	28	n.d.[d]	>99
3	$CHCl_3$	K_2CO_3[f]	35	32	27	>99
4	$CHCl_3$	$(Et)_3N$[e]	77	20	n.d.[d]	>99
5	CH_2Cl_2	$(Et)_3N$[e]	62	32	n.d.[d]	>99
6	DMF	$(Et)_3N$[e]	54	31	~7	3.7
7	CH_3CN	$(Et)_3N$[e]	48	25	21	2.4
8	MeOH	$(Et)_3N$[e]	42	31	22	2.8

[a] 3.5 equiv. *tert*-butyl bromoacetate, 14–20 h, 298 K.
[b] Isolated yield of purified product.
[c] Ratio of 1,4/1,7 bis-alkylated cyclen determined by ^1H NMR and ^{13}C NMR.[21]
[d] Not detect.
[e] 10.0 equiv. of $(Et)_3N$ or pyridine.
[f] 5.0 equiv. of K_2CO_3.

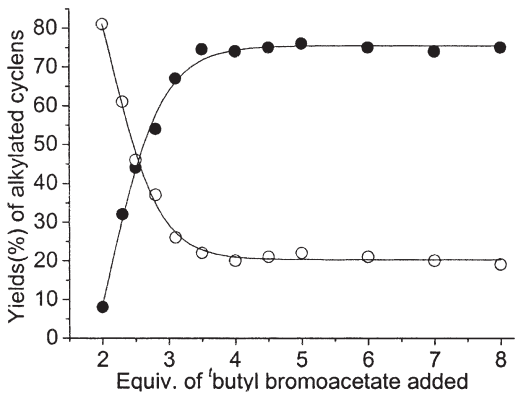
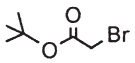
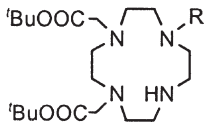
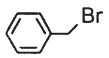
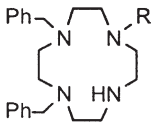
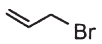
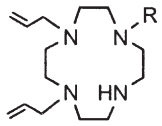
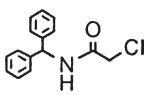
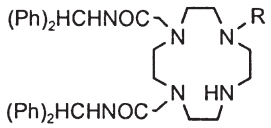
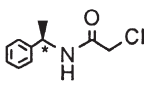
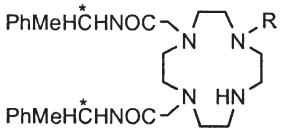
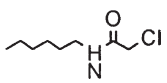
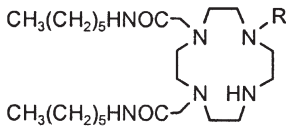
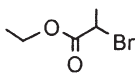
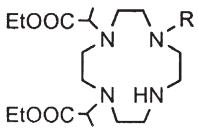


Figure 2. Plot of yields of tris and 1,4-bis *N*-alkylated cyclens 1 (●) and 1a (○) as a function of the number of equivalents of *tert*-butyl bromoacetate added (298 K, $CHCl_3/(Et)_3N$).

To demonstrate the generality of this protocol in the $CHCl_3/(Et)_3N$ system, selected alkylating agents, especially those that have been widely used as chelating moieties **2b**–**7b**, were examined with cyclen, respectively (Table 2). As expected, corresponding tris *N*-alkylated cyclens **2**–**7** and 1,4-bis *N*-alkylated cyclens **2a**–**7a** were obtained with good yields in the presence of 3.5 and 2.0 equiv. of electrophiles, respectively, with no detection of 1,7-bis and tetra *N*-alkylated cyclens at the same time.

Compounds **1** and **1a** were crystallized from a mixture of 9:1 acetone/H_2O by slow evaporation. Interestingly, single crystal X-ray structures demonstrated that both **1** and **1a** were in the form of their mono hydrochloride salts. In

Table 2. Yield and regioselectivity of selected electrophiles with cyclen in the condition of $CHCl_3/(Et)_3N$

Entry	Electrophiles	Product	Yield (%)[a]
1	**1b** 		**1**. R=CH_2COOBu^t Tris: 77[b] **1a**. R=H 1,4-Bis: 81[c], *r*>99[d]
2	**2b** 		**2**. R=CH_2Ph Tris: 86%[b] **2a**. R=H 1,4-Bis: 78[c], r>99[d]
3	**3b** 		**3**. R=$CH_2CH{=}CH_2$ Tris: 76%[b] **3a**. R=H 1,4-Bis: 73[c], *r*>99[d]
4	**4b** 		**4**. R=$CH_2CONHCH(Ph)_2$ Tris: 81[b] **4a**. R=H 1,4-Bis: 71[c], *r*>99[d]
5	**5b** 		**5**. R=$CH_2CONH\overset{*}{C}HMePh$ Tris: 71[b] **5a**. R=H 1,4-Bis: 73[c], *r*>99[d]
6	**6b** 		**6**. R=$CH_2CONH(CH_2)_5CH_3$ Tris: 84[b] **6a**. R=H 1,4-Bis: 75[c], *r*>99[d]
7	**7b** 		**7**. R=CHMeCOOEt Tris: 65[b] **7a**. R=H 1,4-Bis: 70[c]

[a] Isolated yield of purified product.
[b] In presence of 3.5 equiv. of halides.
[c] In presence of 2.0 equiv. of halides.
[d] Ratio of 1,4/1,7 *N*-alkylated cyclen.

previous reports of the crystal structure of DO3A[23] or DOTA derivatives[24], the 12-membered cyclen rings usually adopted a square [3333] conformation (A, Fig. 5). However, the common feature of both **1** and **1a** is that an unalkylated N atom on the cyclen ring is protonated, and H-bonds with the opposite N atom. This H-bonding results in the square macrocycle ring being 'pressed' to the rectangular [2424] conformations (B, Fig. 5). In the structure of **1**·HCl[25] (Fig. 3), hydrogen bonding interaction was found between N(1) and protonated N(3), with a bonding distance of 3.032 Å, and the N–H···N angle was 150.2°. We propose that its protonation prevents N(3) on the cyclen from being alkylated, even in the presence of a large excess of electrophiles. In the structure of **1a**·HCl[26] (Fig. 4), H-bonding developed between the unalkylated N(3) and opposite N(1), with a distance of 2.867 Å, which was even shorter than that in **1**·HCl, and the N–H···N angle was 153.5°. For the two neighboring unalkylated amines in **1a**, N(3) was protonated and H-bonded with opposite N(1); meanwhile, the nucleophilicity of N(4) decreased substantially due to its intraannular lone pair, which might explain why part of 1,4-bis *N*-alkylated products can not be transformed to the tris or tetra *N*-alkylated products even in excess of electrophiles.

3. Conclusion

In conclusion, we developed a general one-step synthetic strategy to prepare the tris *N*-alkylated cyclens in a yield of up to 86%. This unique regioselectivity can be well understood by the single crystal structures of **1** and **1a**. Under the $CHCl_3/(Et)_3N$ reaction condition, nitrogen atoms in the macrocycle can be selectively protonated, which prevents its further alkylation even in a large excess of electrophile, and ultimately gives rise to this regioselectivity. As far as we are aware, this is the first time that the 12-membered cyclen ring has been observed to

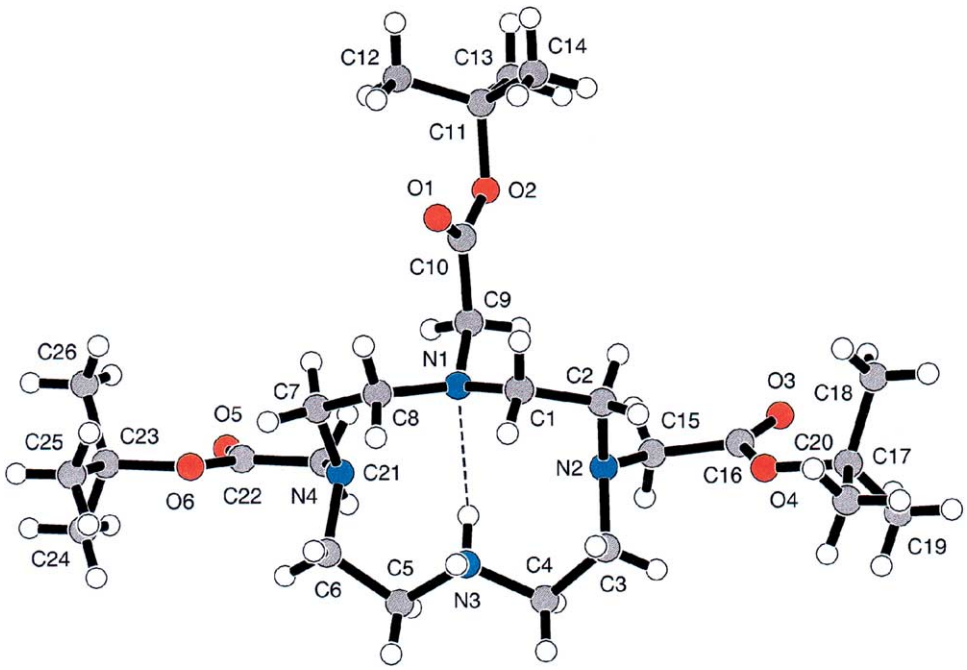


Figure 3. X-ray crystal structure of **1**.

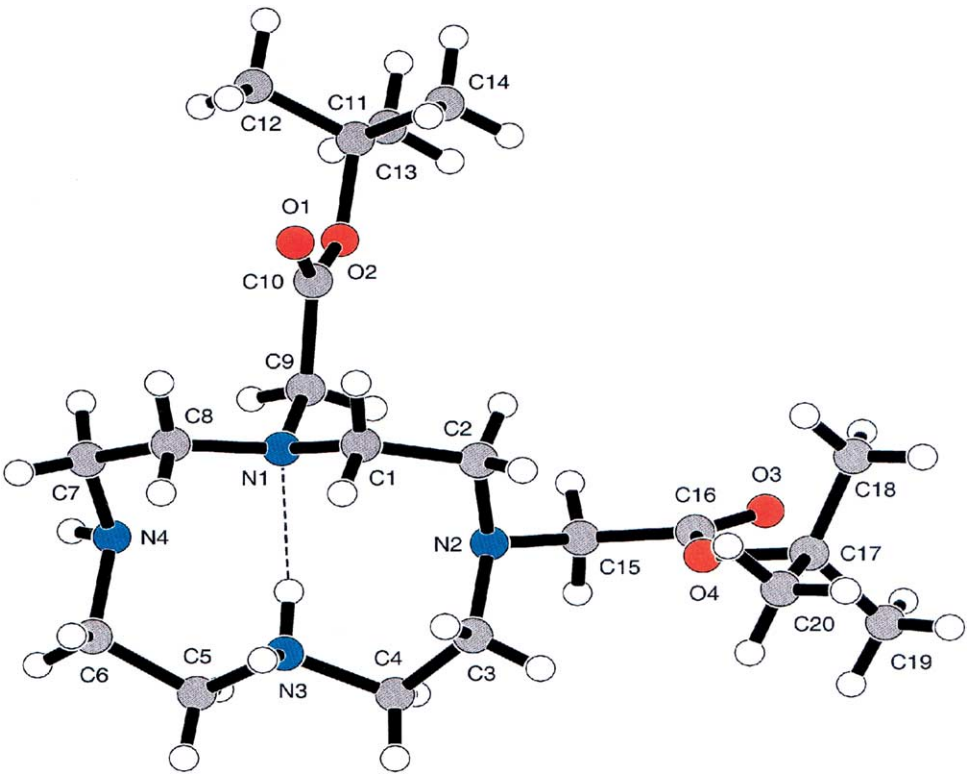


Figure 4. X-ray crystal structure of **1a**.

change from square to rectangular conformations via intraannular H-bonding (Fig. 5). The attractive features of this method such as high yield, operational convenience, cost and labor economy will provide more opportunities to create novel ligands based on tris *N*-alkylated cyclen derivatives, and thus facilitate the application of lanthanide complexes in drug discovery.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere using oven-dried glassware. $CHCl_3$ and CH_2Cl_2 were distilled from calcium hydride and stored over 4 Å

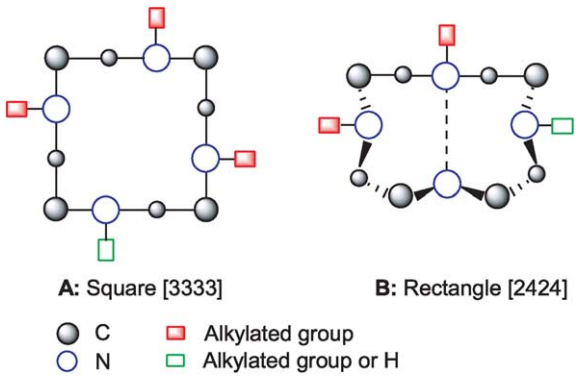


Figure 5. Conformations of 12-membered cyclen ring.

molecular sieves. Triethylamine were distilled from calcium hydride and stored over sodium hydroxide. Flash chromatography was performed on aluminum oxide 90 active neutral (particle size 70–230 mesh) using $CHCl_3/CH_3OH$ as eluting solvents. NMR spectra were measured in $CDCl_3$ or CD_3OD with $SiMe_4$ as an internal standard at ambient temperature on a Bruker Avance DPX 300 or 400 Fourier Transform Spectrometer. Mass spectra were obtained at a Finnigan MAT 95 mass spectrometer for high resolution Fast Atom Bombardment (FAB) mass spectra, and at a LCQ quadrupole ion trap mass spectrometer for low resolution Electron Spray Ionization source (ESI) mass spectra. Elemental analyses were performed in the Department of Chemistry, City University of Hong Kong.

4.2. General method for tris-*N* alkylated-1,4,7,10-tetraazacyclododecane (1–7)

3.5 equiv. of appropriate electrophile (7.6 mmol) dissolved in 10.0 mL of anhydrous chloroform was added dropwise to a mixture of 1,4,7,10-tetraazacyclododecane (cyclen) (400.0 mg, 2.32 mmol) and 10.0 equiv. triethylamine (2.3 g, 23.2 mmol) in 40 mL of anhydrous chloroform under argon atmosphere. The reaction mixture was stirred for a further 16–20 h. The resulting solution was washed by water (3×40 mL), and the organic phase was dried by Na_2SO_4. The solvent was removed, and the crude products were purified by column chromatography on Al_2O_3 to afford the products **1**–**7**.

4.2.1. Tris-(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane·HCl (1). 1 was prepared as a white solid (0.98 g, 1.79 mmol); yield 77% mp 178–180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (4H, s), 3.26 (2H, s), 3.05 (4H, s), 2.89–2.85 (12H, m), 1.47 (27H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (2×C), 169.6 (C), 81.6 (3×C), 58.2 (3×CH_2), 51.3 (2×CH_2), 51.1 (2×CH_2), 49.2 (2×CH_2), 47.5 (2×CH_2), 28.2 (3×CH_3), 28.1 (6×CH_3); ESI-MS *m/z* 515 $(M+H)^+$; HRFAB-MS calcd for $C_{26}H_{51}N_4O_6$ $(M+H)^+$ 515.3809; found 515.3811. Anal. calcd for $C_{26}H_{51}N_4O_6Cl$: C, 56.66; H, 9.33; N, 10.17. Found: C, 56.41; H, 9.61; N, 10.34.

4.2.2. Tris-(benzyl)-1,4,7,10-tetraazacyclododecane·HCl (2). 2 was prepared as a colorless oil (0.96 g, 2.00 mmol), yield 86% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.30 (8H, m), 7.28–7.22 (2H, m), 7.21–7.13 (3H, m), 6.90 (2H, d, *J*=6.8 Hz), 3.65 (4H, s), 3.35 (2H, s), 2.83–2.57 (16H, br, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8 (2×C), 138.1 (C), 129.6 (2×CH), 129.5 (4×CH), 128.2 (4×CH), 128.1 (2×CH), 127.6 (2×CH), 127.0 (CH), 62.2 (2×CH_2), 51.8 (CH_2), 51.2 (2×CH_2), 50.8 (2×CH_2), 50.2 (2×CH_2), 48.2 (2×CH_2); ESI-MS *m/z* 443 $(M+H)^+$; HRFAB-MS calcd for $C_{29}H_{39}N_4$ $(M+H)^+$ 443.3175, found 443.3171. Anal. calcd for $C_{29}H_{39}N_4Cl$: C, 72.70; H, 8.20; N, 11.69. Found: C, 72.56; H, 8.36; N, 11.42.

4.2.3. Tris-(allyl)-1,4,7,10-tetraazacyclododecane·HCl (3). 3 was prepared as a colorless oil (579 mg, 1.76 mmol), yield 76% ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80–5.70 (3H, m), 5.14–5.06 (6H, m), 3.11 (6H, d, *J*=6.4 Hz), 2.73–2.50 (16H, br, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7 (2×CH), 130.8 (CH), 119.8 (CH_2), 118.6 (2×CH_2), 60.7 (2×CH_2), 50.3 (2×CH_2), 49.7 (2×CH_2), 49.0 (2×CH_2), 48.7 (2×CH_2), 47.9 (CH_2); ESI-MS *m/z* 293 $(M+H)^+$; HRFAB-MS calcd for $C_{17}H_{33}N_4$ $(M+H)^+$, 293.2705, found 293.2714. Anal. calcd for $C_{17}H_{33}N_4Cl$: C, 62.08; H, 10.11; N, 17.03. Found: C, 62.16; H, 10.36; N, 16.82.

4.2.4. Tris-[(diphenyl)methylcarbamoylmethyl]-1,4,7,10-tetraazacyclododecane·HCl (4). 4 was prepared as a colorless oil (1.65 g, 1.88 mmol), yield 81% ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66–8.60 (2H, br), 7.85–7.82 (1H, br), 7.22–7.06 (30H, m), 6.18 (2H, d, *J*=6.3 Hz), 5.97 (1H, d, *J*=6.3 Hz), 3.27–3.17 (6H, m), 2.72–2.25 (16H, br, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (2×C), 171.3 (C), 141.8 (4×C), 141.7 (2×C), 129.1 (12×CH), 128.1 (12×CH), 127.8 (6×CH), 59.7 (3×CH), 58.2 (3×CH_2), 51.3 (2×CH_2), 51.1 (2×CH_2), 49.2 (2×CH_2), 47.5 (2×CH_2); ESI-MS *m/z* 842 $(M+H)^+$; HRFAB-MS calcd for $C_{53}H_{60}N_7O_3$ $(M+H)^+$, 842.4758, found 842.4776. Anal. calcd for $C_{53}H_{60}N_7O_3Cl$: C, 72.46; H, 6.88; N, 11.16. Found: C, 72.25; H, 6.65; N, 11.12.

4.2.5. Tris-[(*R*)-1-(1-phenyl)ethylcarbamoylmethyl]-1,4,7,10-tetraazacyclododecane·HCl (5). 5 was prepared as a colorless oil (1.14 g, 1.65 mmol), yield 71% ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51–8.45 (2H, br), 8.16–8.12 (1H, br), 7.39–7.04 (15H, m), 5.04–4.80 (3H, m), 3.28–3.03 (6H, br, s), 2.73–2.22 (16H, br, m), 1.45 (9H, br, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (C), 170.8 (C), 170.6 (C), 144.1 (C), 143.8 (2×C), 128.4 (6×CH), 127.1 (3×CH), 126.4 (6×CH), 60.7 (2×CH_2), 60.6 (CH_2), 54.2 (2×CH_2), 53.2 (2×CH_2), 52.1 (2×CH_2), 48.9 (CH), 48.7 (2×CH), 46.7 (2×CH_2), 22.5 (CH_3), 21.8 (2×CH_3); ESI-MS *m/z* 656 $(M+H)^+$; HRFAB-MS calcd for $C_{38}H_{54}N_7O_3$ $(M+H)^+$, 656.4288, found 656.4284. Anal. calcd for $C_{38}H_{54}N_7O_3$-$Cl{\cdot}H_2O$: C, 64.25; H, 7.95; N, 13.80. Found: C, 64.44; H, 7.79; N, 13.99.

4.2.6. Tris-(hexylcarbamoylmethyl)-1,4,7,10-tetraazacyclododecane·HCl (6). 6 was prepared as a colorless oil (1.23 g, 1.95 mmol), yield 84% ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95–7.72 (3H, br, m), 3.14–3.10 (12H, br, s), 2.75–2.63 (8H, br, m), 2.60–2.46 (8H, br, m), 1.43–1.41 (6H, br, m), 1.23–1.10 (18H, br, s), 0.77 (9H, br, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (C), 170.9 (2×C), 60.7 (3×CH_2), 56.2 (CH_2), 55.1 (CH_2), 53.2 (2×CH_2), 52.6 (2×CH_2), 47.1 (2×CH_2), 39.5 (CH_2), 39.4 (2×CH_2), 31.4

(2×CH_2), 31.3 (CH_2), 29.5 (2×CH_2), 29.4 (CH_2), 26.6 (2×CH_2), 26.4 (CH_2), 22.4 (3×CH_2), 13.8 (3×CH_3); ESI-MS *m/z* 596 $(M+H)^+$; HRFAB-MS calcd for $C_{32}H_{66}N_7O_3$ $(M+H)^+$, 596.5227, found 596.5235. Anal. calcd for $C_{32}H_{66}N_7O_3Cl$: C, 60.78; H, 10.52; N, 15.50. Found: C, 60.94; H, 10.69; N, 15.55.

4.2.7. Tris-[ethyloxycarbonyl-1-methylmethyl]-1,4,7,10-tetraazacyclododecane·HCl (7) (racemic mixture). 7 was prepared as a colorless oil (0.71 g, 1.51 mmol), yield 65%. ^1H NMR (400 MHz, $CDCl_3$): δ 4.04 (6H, br, s), 3.54–3.50 (1H, m), 3.36–3.32 (2H, m), 3.03–2.36 (16H, br, m), 1.28–1.06 (18H, m); ESI-MS *m/z* 473 $(M+H)^+$; HRFAB-MS calcd for $C_{23}H_{45}N_4O_6$ $(M+H)^+$, 473.3339, found 473.3336. Anal. calcd for $C_{23}H_{45}N_4O_6Cl{\cdot}H_2O$: C, 52.41; H, 8.99; N, 10.63. Found: C, 52.15; H, 8.79; N, 10.47.

4.3. General method for 1,4-bis *N*-alkylated-1,4,7,10-tetraazacyclododecane 1a–7a

2.0 equiv. of appropriate electrophiles (4.64 mmol) dissolved in 10.0 mL anhydrous chloroform was added dropwise to a mixture of 1.0 equiv. 1,4,7,10-tetraazacyclododecane (cyclen) (400.0 mg, 2.32 mmol) and 10.0 equiv. triethylamine (2.32 g, 23.20 mmol) in 40 mL anhydrous chloroform under a N_2 atmosphere for approximately half an hour. The reaction mixture was allowed to continuously stir for a further 12–14 h. The resulting solution was washed by water (3×40 mL) then the organic phase was dried by Na_2SO_4. The solvent was removed, and the crude products were purified by column chromatography on Al_2O_3 to afford the products **1a–7a**.

4.3.1. 1,4-Bis (*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane·HCl (1a). 1a was prepared as a white power solid (821 mg, 1.88 mmol); yield 81% ^1H NMR (400 MHz, $CDCl_3$): δ 3.32 (4H, s), 2.98–2.96 (8H, m), 2.89–2.87 (8H, m), 1.41 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (C), 81.6 (2×C), 53.4 (2×CH_2), 51.1 (2×CH_2), 49.9 (2×CH_2), 46.5 (2×CH_2), 46.1 (2×CH_2), 28.2 (6×CH_3); IR (KBr, cm^{-1}) 2976, 1732, 1715, 1636, 1559, 1457, 1167; ESI-MS *m/z* 401 $(M+H)^+$; HRFAB-MS calcd for $C_{20}H_{41}N_4O_4$ $(M+H)^+$, 401.3128, found 401.3130. Anal. calcd for $C_{20}H_{41}N_4O_4Cl$: C, 54.97; H, 9.46; N, 12.82. Found: C, 55.07; H, 9.76; N, 12.57.

4.3.2. 1,4-Bis (benzyl)-1,4,7,10-tetraazacyclododecane·HCl (2a). 2a was prepared as a colourless oil (704 mg, 1.81 mmol); yield 78%. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28–7.16 (10H, m), 3.51 (4H, s), 2.85 (4H, br, s), 2.80–2.74 (4H, m), 2.67–2.61 (4H, m), 2.57 (4H, br, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0 (2×C), 129.9 (4×CH), 128.8 (4×CH), 127.6 (2×CH), 57.6 (2×CH_2), 51.5 (2×CH_2), 51.2 (2×CH_2), 47.1 (2×CH_2), 46.2 (2×CH_3); ESI-MS *m/z* 353 $(M+H)^+$; HRFAB-MS calcd for $C_{22}H_{33}N_4$ $(M+H)^+$, 353.2705, found 353.2711. Anal. calcd for $C_{22}H_{33}N_4Cl$: C, 67.93; H, 8.55; N, 14.40. Found: C, 67.66; H, 8.51; N, 14.71.

4.3.3. 1,4-Bis (allyl)-1,4,7,10-tetraazacyclododecane·HCl (3a). 3a was prepared as a white power solid (488 mg, 1.69 mmol); yield 73%. ^1H NMR (400 MHz, $CDCl_3$): δ 5.62–5.51 (2H, m), 4.92–4.86 (4H, m), 2.89–2.87 (4H, d, *J*=6.4 Hz), 2.62 (4H, br, s), 2.52–2.47 (4H, m), 2.38–2.35 (4H, m), 2.31 (4H, br, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9 (2×CH), 118.1 (2×CH_2), 55.4 (2×CH_2), 50.5 (2×CH_2), 50.0 (2×CH_2), 46.6 (2×CH_2), 45.5 (2×CH_2); ESI-MS *m/z* 253 $(M+H)^+$; HRFAB-MS calcd for $C_{14}H_{29}N_4$ $(M+H)^+$, 253.2392, found 253.2384. Anal. calcd for $C_{14}H_{29}N_4Cl$: C, 58.21; H, 10.12; N, 19.40. Found: C, 58.41; H, 9.89; N, 19.22.

4.3.4. 1,4-Bis-[(diphenyl)methylcarbamoylmethyl]-1,4,7,10-tetraazacyclododecane·HCl (4a). 4a was prepared as a colorless oil (1.13 g, 1.65 mmol); yield 71% ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.07 (20H, m), 6.21 (2H, m), 3.19 (4H, s), 2.64–2.17 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (2×C), 142.1 (4×C), 128.9 (8×CH), 128.1 (4×CH), 127.7 (8×CH), 59.4 (2×CH_2), 52.5 (2×CH_2), 51.3 (2×CH_2), 50.3 (2×CH), 48.5 (2×CH_2), 47.5 (2×CH_2); ESI-MS *m/z* 647 $(M+H)^+$; HRFAB-MS calcd for $C_{38}H_{47}N_8O_2$ $(M+H)^+$, 647.3822, found 647.3829. Anal. calcd for $C_{38}H_{47}N_8O_2Cl$: C, 66.80; H, 6.93; N, 16.40. Found: C, 66.51; H, 6.66; N, 16.11.

4.3.5. 1,4-Bis-[(*R*)-1-(1-phenyl)ethylcarbamoylmethyl]-1,4,7,10-tetraazacyclododecane·HCl (5a). 5a was prepared as a colorless oil (898 mg, 1.69 mmol); yield 73% ^1H NMR (400 MHz, CD_3OD): δ 7.37–7.10 (10H, m), 5.04–4.92 (2H, m), 3.26–3.07 (4H, q, *J*=8.2, 6.3 Hz), 2.75–2.60 (16H, m), 1.52 (6H, d, *J*=7.0 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 171.6 (2×C), 143.8 (2×C), 128.6 (4×CH), 127.0 (2×CH), 126.1 (4×CH), 57.3 (2×CH_2), 52.7 (2×CH_2), 48.6 (2×CH_2), 48.0 (2×CH), 45.7 (2×CH_2), 44.9 (2×CH_2), 21.1 (2×CH_3); ESI-MS *m/z* 495 $(M+H)^+$; HRFAB-MS calcd for $C_{28}H_{43}N_6O_2$ $(M+H)^+$, 495.3447, found 495.3451. Anal. calcd for $C_{28}H_{43}N_6O_2Cl$: C, 63.32; H, 8.16; N, 15.82. Found: C, 63.57; H, 8.27; N, 15.77.

4.3.6. 1,4-Bis-[(hexylcarbamoylmethyl)-1,4,7,10-tetraazacyclododecane·HCl (6a). 6a was prepared as a colorless oil (886 mg, 1.74 mmol); yield 75% ^1H NMR (400 MHz, $CDCl_3$): δ 3.32 (4H, s), 3.22–3.11 (4H, br, m), 2.85–2.70 (8H, m), 2.63–2.47 (8H, m), 1.61–1.47 (4H, br, s), 1.40–1.27 (12H, br, s), 0.88 (6H, br, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2 (C), 172.2 (C), 57.5 (CH_2), 56.3 (CH_2), 52.5 (2×CH_2), 52.0 (2×CH_2), 45.3 (2×CH_2), 44.3 (2×CH_2), 39.2 (CH_2), 39.0 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 22.2 (2×CH_2), 13.0 (CH_2), 12.9(CH_2); ESI-MS *m/z* 455 $(M+H)^+$; HRFAB-MS calcd for $C_{24}H_{51}N_6O_2$ $(M+H)^+$, 455.4074, found 455.4065. Anal. calcd for $C_{24}H_{51}N_6O_2Cl{\cdot}H_2O$: C, 56.61; H, 10.49; N, 16.51. Found: C, 56.38; H, 10.42; N, 16.33.

4.3.7. 1,4-Bis-(ethyloxycarbonyl-1-methylmethyl)-1,4,7,10-tetraazacyclododecane·HCl (7a) (racemic mixture). 7a was prepared as a colorless oil (677 mg, 1.62 mmol); yield 70% ^1H NMR (400 MHz, $CDCl_3$): δ 4.01 (4H, br, s), 3.43–3.40 (2H, m), 3.03–2.36 (16H, br, m), 1.28–1.06 (12H, m); ESI-MS *m/z* 373.3 $(M+H)^+$; HRFAB-MS calcd for $C_{18}H_{37}N_4O_4$ $(M+H)^+$, 373.2815, found 373.2825. Anal. calcd for $C_{18}H_{37}N_4O_4Cl{\cdot}0.5\ H_2O$: C, 51.73; H, 9.16; N, 13.40. Found: C, 51.59; H, 9.33 N, 13.12.

4.3.8. X-ray crystallography. Data collections were performed at 20 °C with a Bruker AXS SMART 1000

CCD diffractometer that was interfaced with a Silicon Graphics INDY™ workstation using the program package TeXsan from MSC (version 1.7–2.0). The structures were solved by direct methods (SIR92 or ORIENT), and refined by full-matrix least-squares methods on *F* (teXsan). Crystallographic data for compound **1** and **1a** have been deposited with the Cambridge Crystallographic Data Centre (Deposition numbers CCDC 206158 and 206159). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam).

Acknowledgements

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21. In the ^{13}C NMR spectral, 1,7 bis *N*-alkylated adduct displays two carbon signals for the eight carbons of the cyclen ring indicating a D_{2h} symmetry whereas 1,4 bis *N*-alkylated adduct displays four carbon signals indicating C_{2v} symmetry.
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25. Crystal data for **1**·HCl: $C_{26}H_{52}ClN_4O_{6.50}$, M=561.18, monoclinic, space group $P2/c$ (#13), a=22.076(4), b=6.699(1), c=23.700(4) Å, β=111.55(1)°, V=3259.9(9) Å^3, Z=4, $D_{calc.}$=1.143 g/cm^3, μ(Mo Kα)=0.159 cm^{-1}, T=298 K, 20143 reflections collected, 7922 unique (R_{int}=0.023). Refinement on F, final $R1$=0.0459 (for 4274 reflections with $I \geq 2.00\sigma(I)$), $wR2$=0.0562.
26. Crystal data for **1a**·HCl: $C_{40}H_{88}Cl_2N_8O_{11}$, M=928.09, tetragonal, space group $P\bar{4}$ (#81), a=28.798(3), b=28.798 (3), c=6.407(1) Å, V=5313.5(10) Å^3, Z=4, D_{calc}=1.160 g/cm^3, μ (Mo Kα)=0.179 cm^{-1}, T=298 K, 33108 reflections collected, 6576 unique (R_{int}=0.051). Refinement on F, final $R1$=0.0735 (for 3768 reflections with $I \geq 2.00\sigma(I)$), $wR2$=0.1081 (for 3768 reflections).

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Domino carbocationic rearrangements of α-[bis(methylthio)methylene]alkyl-2-(heteroaryl)cyclopropyl ketones

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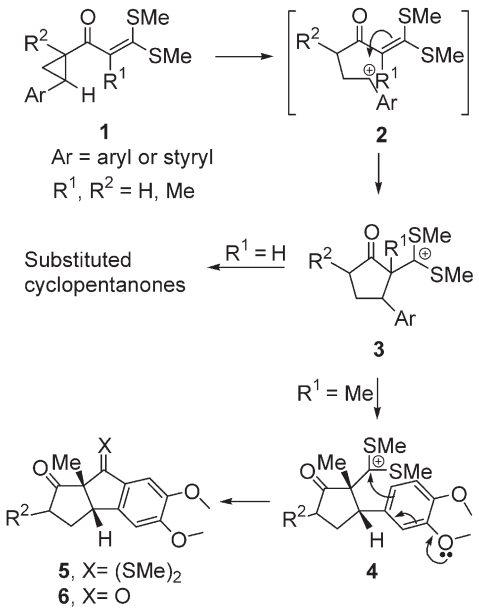
Dedicated to Dr. Sukh Dev on his 80th birthday

Abstract—Domino carbocationic rearrangements of α-[bis(methylthio)methylene]alkyl-2-(heteroaryl)cyclopropyl ketones (X=O, S, NMe) bearing five-membered heteroaryl group have been investigated. Although the cyclopropyl ketones (R^1=H) gave similar products like their aryl counterparts under these conditions, the corresponding α-methylcyclopropyl ketones (R^1=Me) yielded a variety of unexpected products depending on the nature of heteroaryl group in the substrate cyclopropyl ketones and the type of acid catalyst used. A probable mechanism for the formation of various products in these transformations has been proposed.

1. Introduction

The search for new and efficient methodologies that allow rapid construction of polycyclic frameworks in a single operation offers important synthetic challenge to organic chemists.[1] In this regard, carbocationic cyclization of polyolefinic precursors has emerged as an extremely powerful synthetic method for construction of fused cyclohexane rings in high yields with good stereocontrol.[2] However, application of cascade carbocationic olefinic cyclizations for the synthesis of fused cyclopentanoids has been less common,[3–5] despite the widespread occurrence of these structural frameworks in biologically important natural products.[6] We have shown in our earlier studies that the cyclopropyl ketones of the general structure **1** undergo electrophilic ring opening in the presence of Lewis or protic acids to give carbocationic intermediate **2** which is intramolecularly captured by electron rich ketene dithioacetal double bond in an 5-*exo* fashion resulting in the formation of a cyclopentanone ring with a pendant 2-[bis(methylthio)methyl] carbocation **3**.[7] The intermediate **3** is quenched by a variety of processes depending on the reaction conditions and the structure of cyclopropyl ketones (R^1=H or Me) providing an efficient new route for substituted cyclopentanones. Subsequently we have demonstrated that the stable carbocationic intermediate **3** with a α-methyl group (R^1=Me) can be intercepted in a domino fashion by a pendant electron rich arene (**4**) or by an olefinic double bond to furnish cyclopenta[*b*]indane **5**–**6**[8a] or diquinane[8b] derivatives in highly stereoselective fashion (Scheme 1). Similar domino carbocationic rearrangements of the related cyclopropyl carbinols affording either cyclopenta[*b*]indane,[8b] bicyclo[3.2.1]octene[8c] or 1-aryl-



Scheme 1.

Keywords: Heteroarylcyclopropyl ketones; Domino carbocationic rearrangement; α-Oxoketene dithioacetals; Cyclopentano[*b*]fused heterocycles.
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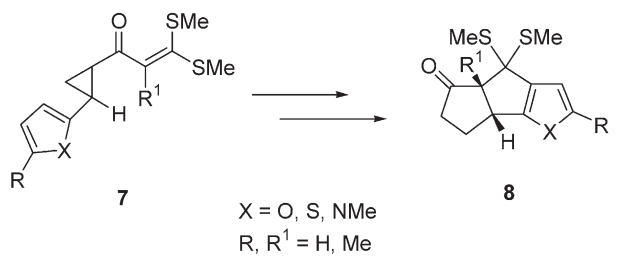
indane[9a] frameworks have also been described. During the course of our continued interest in the design and elaboration of new carbocationic domino process,[9b,c] we further became interested in examining acid induced domino carbocationic cyclization of the substrate cyclopropyl ketones of the general structure **7** bearing a five-membered heteroaryl group. It was speculated that the heteroaryl group in these ketones would act as an efficient cationic cyclization terminator yielding novel pentaleno[*b*]-fused heteroaromatic frameworks (**7→8**) (Scheme 2). However, our studies revealed formation of a variety of products in these reactions depending on the nature of heteroaryl group in the substrate cyclopropyl ketones and

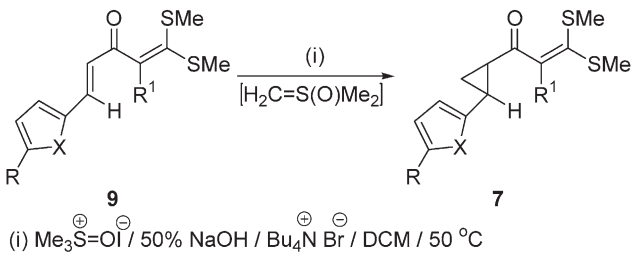


Scheme 2.

the type of acid catalyst used. We now report the results of this investigation along with the probable mechanism for the formation of various products.

2. Results

The starting α-[3-(heteroaryl)propenoyl]ketene dithioacetals **9a–g** were prepared according to the earlier reported procedure.[10] The ketene dithioacetals **9a–g** were transformed into the corresponding cyclopropyl ketones **7a–g** regioselectively in high yields by treatment with dimethyloxosulfonium methylide in the presence of phase transfer catalyst[7c] (Table 1, Scheme 3). The structures of **7a–g** were fully confirmed with the help of spectral and analytical data.



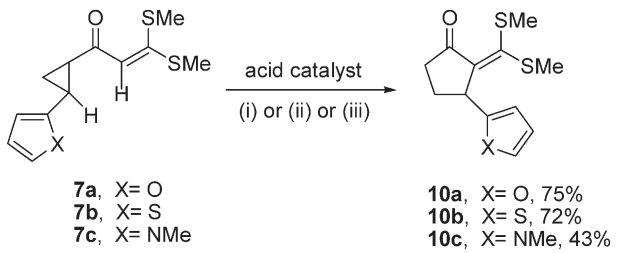
Scheme 3.

Table 1.

9, **7**	R	R^1	X	Yield
9, **7a**	H	H	O	92%
9, **7b**	H	H	S	94%
9, **7c**	H	H	NMe	70%
9, **7d**	H	Me	O	91%
9, **7e**	Me	Me	O	94%
9, **7f**	H	Me	S	91%
9, **7g**	H	Me	NMe	89%

2.1. Domino carbocationic rearrangements of cyclopropyl ketones 7a–c

The carbocationic rearrangements of cyclopropyl ketones **7a–c** without α-methyl group were first investigated in the presence of common Lewis/protic acids under various conditions which have been successfully applied for the previously described 5-*exo* cyclization of 2-arylcyclopropyl ketones **1** (Scheme 4).[7] However, these ketones with acid labile 2-furyl-(**7a**) and 2-(1-*N*-methylpyrrolyl)-(**7c**) groups were found to be unstable on treatment with various electrophilic reagents at room temperature or under more drastic conditions yielding either polymeric or intractable reaction mixtures. Under optimized milder conditions, the cyclopropyl ketones **7a–b** could be transformed into the expected 3-(heteroaryl)-2-[bis(methylthio)methylene]-cyclopentanones **10a–b** in good yields as shown in Scheme 4. Thus treatment of **7a** with $BF_3{\cdot}Et_2O$ in benzene at 0 °C followed by warming at room temperature led to 3-(2-furyl)-2-[bis(methylthio)methylene] cyclopentanone (**10a**) in 75% yield. Similarly, the reaction of **7b** with stannic chloride at 0 °C in nitromethane furnished the corresponding 3-(2-thienyl)cyclopentanone derivative **10b** in 72% yield. On the other hand, no identifiable product could be isolated when the 2-(1-*N*-methyl-2-pyrrolyl)-cyclopropyl ketone **7c** was exposed to various common Lewis acids ($BF_3{\cdot}Et_2O$, $SnCl_4$, $TiCl_4$) under milder reaction conditions. However, in the presence of Amberlyst-15 resin, the cyclopropyl ketone **7c** was found to rearrange slowly to 2-bis(methylthio)-3-(1-*N*-methyl-2-pyrrolyl)cyclopentanone (**10c**) in moderate yield (43%). The structures of product cyclopentanones **10a–c** were confirmed with the help of spectral and analytical data.

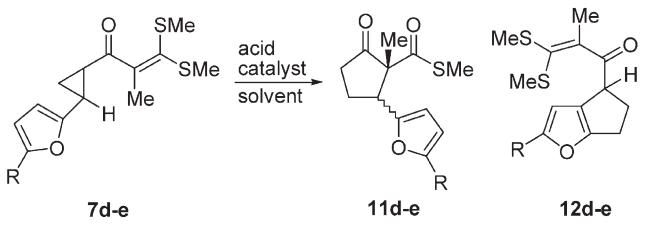


Scheme 4.

2.2. Domino carbocationic rearrangements of cyclopropyl ketones 7d–g

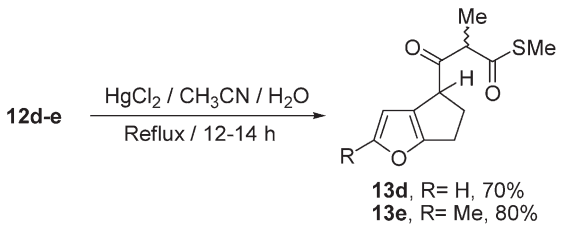
2.2.1. Carbocationic rearrangement of 2-furyl and 2-(5-methylfuryl) cyclopropyl ketones 7d–e. The rearrangements of cyclopropyl ketones **7d–g** bearing the α-methyl group was next investigated (Schemes 5–7). Thus when the cyclopropyl ketone **7d** with a 2-furyl group was exposed to $SnCl_4/CH_3NO_2$ at 0 °C for 4 h, the corresponding 2-(2-furyl)-1-methyl-5-oxocyclopentane-1-carbothioate **11d** was formed in 65% yield (Table 2, entry 1, Scheme 5). However, after prolonged reaction time (12 h), product analysis of the reaction mixture showed formation of a single new product (58%) which was not the expected pentaleno[1,2-*b*]furan **8d** (X=O, R=H, R^1=Me), but was characterized as the

Table 2.



Entry	7	R	Reaction Conditions	Time (h)	Product (% Yield) 11	12
1	**7d**	H	$SnCl_4/CH_3NO_2$/0°C–rt	4	**11d** (65)[a]	–
2	**7d**	H	$SnCl_4/CH_3NO_2$/0°C–rt	12	–	**12d** (58)
3	**7e**	Me	$SnCl_4/CH_3NO_2$/0°C–rt	8	**11e** (25)[a]	**12e** (42)
4	**7e**	Me	$SnCl_4/CH_3NO_2$/0°C–rt	12	–	**12e** (69)
5	**7d**	H	TFA/CH_2Cl_2/0°C–rt	12	**11d** (30)[a]	**12d** (35)
6	**7e**	Me	TFA/CH_2Cl_2/0°C–rt	12	**11e** (30)[a]	**12e** (40)

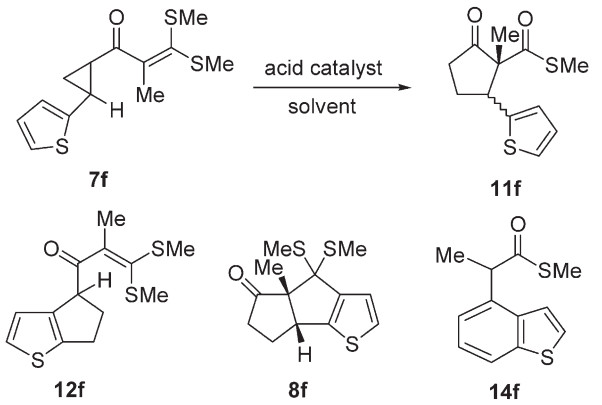
[a] Mixture of diastereomers.



Scheme 5.

4-substituted cyclopenta[*b*]furan derivative **12d** on the basis of its spectral and analytical data (Scheme 5). The reaction of **7d** with TFA/CH_2Cl_2 also gave the products **11d** and **12d** in 30 and 35% yields, respectively (entry 5). Similar results were also obtained with 2-(5-methylfuryl)cyclopropyl ketone **7e** under the influence of either $SnCl_4$ (entries 3, 4) or TFA (entry 6) yielding cyclopenta[*b*]furan derivative **12e** in good yield (69%, entry 4). Our various attempts to obtain pentaleno[*b*] fused furan derivatives **8d–e** (X=O, R=H, Me, R^1=Me) in the presence of various Lewis ($BF_3{\cdot}Et_2O$, $TiCl_4$) and protic (H_3PO_4, PTSA, TfOH) acids under a variety of conditions were, however, not successful. Hydrolysis of **12d–e** in the presence of $HgCl_2/CH_3CN/H_2O$ at reflux temperature afforded the corresponding α-methyl-β-oxocarbothioates **13d–e** in 70 and 80% yields, respectively (Scheme 5).

2.2.2. Carbocationic rearrangement of 2-(2-thienyl)-cyclopropyl ketone 7f. The 2-(2-thienyl)cyclopropyl ketone **7f** was found to be more stable towards various Lewis and protic acids yielding clear-cut products with cleaner work-up procedure (Table 3, Scheme 6). Thus, **7f** behaved in a similar manner as **7d–e** on treatment with either $SnCl_4/CH_3NO_2$ or with TFA affording either *S*-methyl 2-(2-thienyl)-5-oxocyclopentane-1-carbothioate (**11f**) or the cyclopenta[*b*]thiophene **12f** (entries 1 and 3). However, in one case, when **7f** was exposed to $SnCl_4$ for prolonged time (14 h) at 0 °C under identical conditions, work-up and column chromatography of the reaction mixture afforded another new product (10%) (besides **11f** and **12f**), which was characterized as the pentaleno[1,2-*b*]thiophene **8f** on the basis of its spectral and analytical data



Scheme 6.

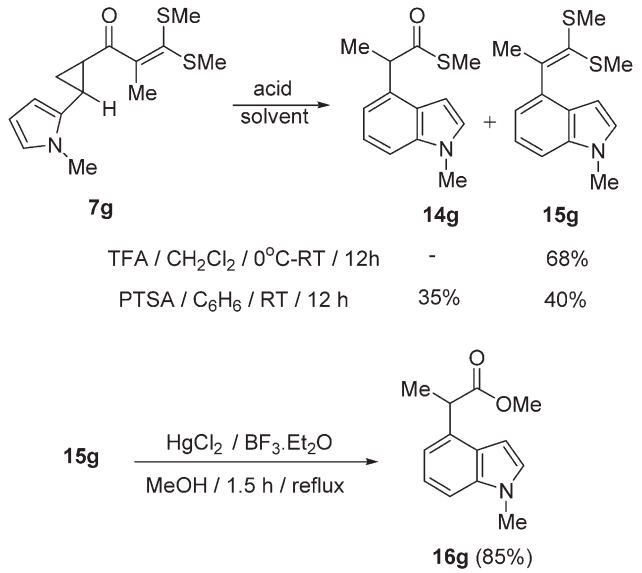
Table 3.

Entry	Reaction Conditions	Time (h)	Product (% Yield) 11f	12f	8f	14f
1	$SnCl_4/CH_3NO_2$/0°C–rt	6	65[a]	–	–	–
2	$SnCl_4/CH_3NO_2$/0°C–rt	14	5[a]	61	10	–
3	TFA/CH_2Cl_2/0°C–rt	14	–	50	–	–
4	H_3PO_4/rt	12	63[a]	–	–	–
5	H_3PO_4/60°C	6	40[a]	–	–	20

[a] Mixture of diastereomers.

(entry 2). Various attempts to increase the yield of product **8f** were, however, not successful. Cationic rearrangement of **7f** could also be effected in H_3PO_4 at room temperature to afford only carbothioate **11f** in 63% yield (entry 4), whereas at higher temperature (60 °C), **11f** was formed in lower yield (40%) along with another product (20%) which was characterized as the cycloaromatized *S*-methyl α-(4-benzothienyl)propane carbothioate **14f** on the basis of its spectral and analytical data (Table 3, entry 5). Attempted hydrolysis of **12f** to β-oxothioate **13f** in the presence of either $HgCl_2/CH_3CN/H_2O$ or $AgNO_3/NCS/CH_3CN/H_2O$ did not give any identifiable product yielding only intractable mixture of products.

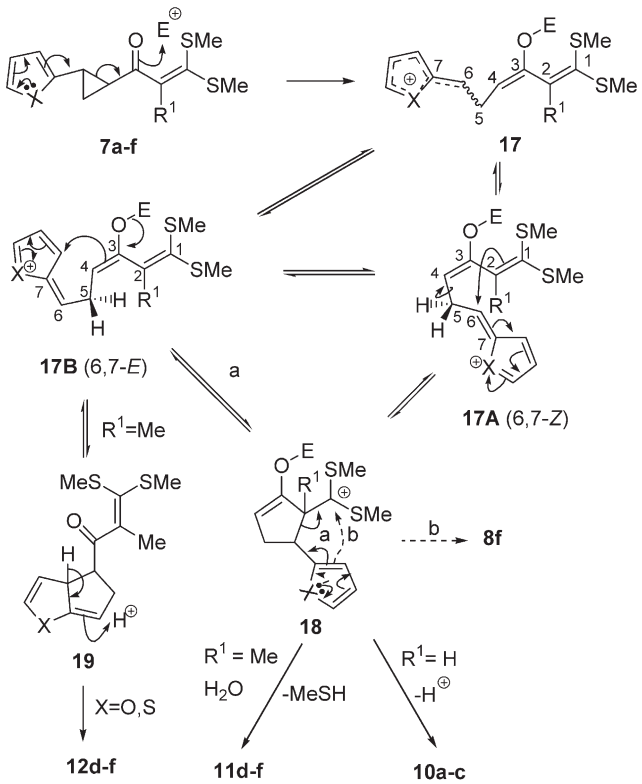
2.2.3. Carbocationic rearrangement of 2-(1-*N*-methyl-2-pyrrolyl)-cyclopropyl ketone 7g. Attempted rearrangement of 2-pyrrolylcyclopropyl ketone **7g** under the influence of various Lewis acids-solvent combinations did not provide any of the expected products formed from the cyclopropyl ketones **7d–f**. In most of the cases, either polymeric or the unidentifiable multiple product mixtures were formed. However, when **7g** was subjected to treatment with TFA, the reaction mixture showed formation of only one product (TLC) which after work-up, isolation and spectroscopic analysis was characterized as 1-*N*-methyl-4-{[1-bis(methylthio)methylene]ethyl}indole (**15g**) formed in 68% yield (Scheme 7). Similarly treatment of **7g** with PTSA in benzene at room temperature afforded **15g** in 40% yield along with the corresponding α-(1-*N*-methyl-4-indolyl)-propane carbothioate **14g** formed by hydrolysis of **15g** under the experimental conditions (Scheme 7). The ketene dithioacetal **15g** could also be converted to the methyl α-(1-*N*-methyl-4-indolyl) propanoate **16g** (85%) on $BF_3{\cdot}Et_2O$ induced methanolysis in the presence of $HgCl_2$ (Scheme 7).



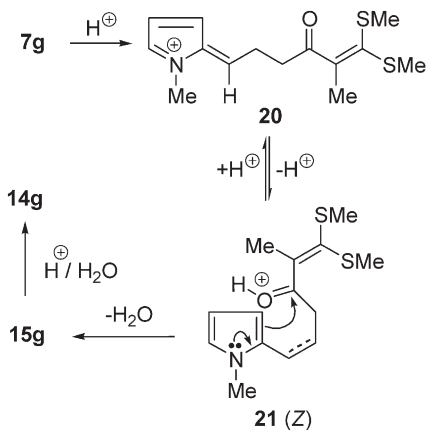
Scheme 7.

3. Discussion

The possible mechanism for the formation of various products **10**–**12** and **14**–**15** from the cyclopropyl ketones **7a**–**g** is depicted in Schemes 8 and 9. Thus the electrophilic ring opening of cyclopropyl ketones **7a**–**f** which is assisted by the heteroatom lone pair electrons of the five-membered heterocycles leads to the formation of stable carbocation **17** (Scheme 8). It appears that the configuration of the *exo*-heterocyclic double bond (6,7) in the carbocation **17** is responsible for the formation of products **11d**–**f** or **12d**–**f**. Thus the *E*-6,7 configuration as depicted in the cation **17B** is



Scheme 8.



Scheme 9.

crucial for the formation of **12d**–**f**, whereas the carbothioates **11d**–**f** seem to be derived from the kinetically favoured **17A** with *Z*-6,7 configuration. Subsequent intramolecular 5-*exo* trapping of **17A** by bis(methylthio)methylene double bond gives cyclopentanone intermediate **18** with a pendant 2-[bis(methylthio)methyl] carbocation which on deprotonation (R^1=H) or hydrolysis (R^1=Me) affords kinetically favoured products **10a**–**c** and **11d**–**f**, respectively, in moderate to good yields as observed in our pervious studies.[7] However, after prolonged time (12–14 h), the cation **17** undergoes different mode of ring closure (through its more stable conformer **17B**) (path a) via intramolecular 5-*exo* nucleophilic attack of the newly generated electron rich dienolate moiety on the electron deficient C-3 position of either furylium (**17B**, X=O) or thiolium (**17B**, X=S) ring to give thermodynamically more stable cyclopenta[*b*]furans (**12d**–**e**) and the corresponding thiophene derivative (**12f**), respectively (Scheme 8). Intramolecular capture of the bis(methylthio)methyl carbocation **18** by C-3 position of either furan or thiophene ring to give rigid pentaleno fused heterocycles **8d**–**f** (path b) appears to be not the facile process in these systems (X=O, S) and **8f** (X=S) was formed only as minor product (10%) on prolonged reaction with $SnCl_4$ (Table 3, entry 2).

The failure of 2-(1-*N*-methyl-2-pyrrolyl)cyclopropyl ketone **7g** to afford domino products similar to those from **7d**–**f** in the presence of various Lewis acids may be attributed to the more labile nature of pyrrole ring towards electrophilic reagents resulting in the formation of polymeric products. However, in the presence of protic acids (TFA or PTSA) under milder reaction conditions, the cation **20** undergoes facile deprotonation and subsequent intramolecular cyclocondensation (through *Z*-vinylpyrrole intermediate **21**) leading to the formation of 4-substituted-1-*N*-methylindole derivative **15g** along with α-[1-*N*-methyl(4-indolyl)]propane carbothioate **14g** formed by in situ hydrolysis of the ketene dithioacetal moiety of **15g**. The related α-(4-benzothienyl)-propane carbothioate **14f** was also isolated as minor product in H_3PO_4 induced rearrangement of 2-thienylcyclopropyl ketone **7f** at 60 °C (Scheme 6, Table 3, entry 5).

4. Conclusion

In summary, domino carbocationic rearrangements of

2-heteroarylcyclopropyl ketones **7d–g** in the presence of various Lewis and protic acids proceed through several interesting and unexpected pathways depending on the nature of heteroaryl group and the type of acid catalyst used. The formation of cyclopenta[*b*]furans **12d–e** and the corresponding cyclopenta[*b*]thiophene **12f** from the cyclopropyl ketones **7d–e** and **7f** via intramolecular nucleophilic trapping of the cation **17B** by in situ generated dienolate double bond is to our knowledge unprecedented in furan and thiophene chemistry. We are currently investigating application of this new domino process for construction of new polycyclic skeletons.

5. Experimental

5.1. General

^{1}HNMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and TMS was used as an internal standard. Melting points were uncorrected. Chromatographic purification was conducted by column chromatography using 100–200 mesh silica gel obtained from standard firms. TLC was performed on Merck Silica gel60F_{254} aluminum sheets. Furfural, 5-methylfurfural, $SnCl_4$, TFA, H_3PO_4 (88%), PTSA·H_2O, BF_3·Et_2O and CH_3NO_2 were purchased from Merck and used as such. Thiophene-2-aldehyde,[11] 1-*N*-methylpyrrole-2-aldehyde,[12] and trimethylsulfoxonium iodide[13] were prepared according to the reported methods. The known α-(2-furyl)propenoyl ketene dithioacetal **9a**[10a] and the unknown α-(heteroaryl)-propenoyl ketene dithioacetals **9b–g** were prepared according to the earlier reported procedure.[10]

5.2. General procedure for preparation of cycloproyl ketones 7a–g

A suspension of the appropriate α-oxoketene dithioacetal **9** (10 mmol), trimethylsulfoxonium iodide (2.64 g, 12 mmol), tetrabutylammonium bromide (1.61 g, 5 mmol) in 50% NaOH solution (50 mL) and CH_2Cl_2 (50 mL) were heated with stirring at 50 °C for 8–24 h (monitored by TLC). The organic layer was separated, the aqueous layer after dilution with H_2O (50 mL) was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with H_2O (2×50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford crude residue, which was diluted with EtOAc and filtered off to remove tetrabutylammonium bromide. The filtrate was evaporated to give crude cyclopropyl ketone, which was purified by filtration through a small silica gel column using EtOAc/hexane (1:10) as eluent.

5.2.1. 3,3-Bis(methylthio)-1-[2-(2-furyl)cyclopropyl]-2-propen-1-one (7a). Yield (2.34 g, 92%) as a colourless solid, mp 96–97 °C; [Found: C, 56.71; H, 5.49. $C_{12}H_{14}O_2S_2$ requires C, 56.66; H, 5.55%]; R_f (20% EtOAc/hexane) 0.41; ν_{max}(KBr) 2914, 1640 (C=O), 1578, 1490 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.24 (1H, d, *J*=1.7 Hz, HetArH), 6.27 (1H, dd, *J*=3.2, 1.7 Hz, HetArH), 6.21 (1H, s, C*H*=C(SCH$_3$)$_2$), 6.04 (1H, d, *J*=3.2 Hz, HetArH), 2.55 (1H, ddd, *J*=7.8, 5.1, 4.2 Hz, C*H*–C=O), 2.48 (3H, s, SCH$_3$), 2.46 (3H, s, SCH$_3$), 2.24 (1H, ddd, *J*=7.8, 5.1, 4.2 Hz, C*H*–HetAr), 1.64 (1H, ddd, *J*=3.9, 5.3, 9.0 Hz, CH_2), 1.40 (1H, ddd, *J*=8.2, 6.6, 3.9 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 191.9 (C=O), 163.5 (CH=*C*(SCH$_3$)$_2$), 154.4 (C), 140.7 (CH), 112.9 (*C*H=C(SCH$_3$)$_2$), 110.4 (CH), 104.9 (CH), 30.7 (CH), 21.6 (CH), 17.1 (CH$_2$), 16.3 (SCH$_3$), 14.8 (SCH$_3$); *m*/*z* 254 (34, M$^+$), 239 (77).

5.2.2. 3,3-Bis(methylthio)-1-(2-(2-thienyl)cyclopropyl)-2-propen-1-one (7b). Yield (2.54 g, 94%) as a colourless solid, mp 89–90 °C; [Found: C, 53.39; H, 5.30. $C_{12}H_{14}OS_3$ requires C, 53.30; H, 5.22%]; R_f (20% EtOAc/hexane) 0.39; ν_{max}(KBr) 2913, 1621 (C=O), 1494, 1381 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.04 (1H, d, *J*=5.1 Hz, HetArH), 6.86 (1H, dd, *J*=3.4, 4.8 Hz, HetArH), 6.78 (1H, d, *J*=3.4 Hz, HetArH), 6.18 (1H, s, C*H*=C(SCH$_3$)$_2$), 2.73 (1H, ddd, *J*=9.2, 6.0, 3.9 Hz, C*H*–C=O), 2.45 (3H, s, SCH$_3$), 2.43 (3H, s, SCH$_3$), 2.14 (1H, ddd, *J*=8.0, 4.9, 4.4 Hz, C*H*–HetAr), 1.74 (1H, ddd, *J*=9.0, 5.2, 4.7 Hz, CH_2), 1.32 (1H, ddd, *J*=9.2, 5.2, 3.7 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 191.7 (C=O), 163.6 (CH=*C*(SCH$_3$)$_2$), 145.4 (C), 126.8 (CH), 123.4 (CH), 122.5 (CH), 112.7 (*C*H=C(SCH$_3$)$_2$), 34.2 (CH), 23.8 (CH), 19.5 (CH$_2$), 17.1 (SCH$_3$), 14.8 (SCH$_3$); *m*/*z* 270 (20, M$^+$), 255 (77), 147 (100).

5.2.3. 3,3-Bis(methylthio)-1-[2-(1-*N*-methyl-2-pyrroyl)-cyclopropyl]-2-propen-1-one (7c). Yield (1.87 g, 70%) as a dark red viscous oil; [Found: C, 58.47; H, 6.35; N, 5.30. $C_{13}H_{17}NOS_2$ requires C, 58.39; H, 6.41; N, 5.24%]; R_f (40% EtOAc/hexane) 0.45; ν_{max}(KBr) 2921, 1685 (C=O), 1490 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.52 (1H, t, *J*=2.0 Hz, HetAr), 6.20 (1H, s, C*H*=C(SCH$_3$)$_2$), 5.99 (1H, t, *J*=3.2 Hz, HetAr), 5.77 (1H, dd, *J*=1.7, 3.6 Hz, HetAr), 3.57 (3H, s, NCH$_3$), 2.47 (3H, s, SCH$_3$), 2.45 (3H, s, SCH$_3$), 2.39 (1H, ddd, *J*=4.4, 6.2, 9.4 Hz, C*H*–C=O), 1.99 (1H, ddd, *J*=4.1, 5.0, 8.4 Hz, C*H*–HetAr), 1.63 (1H, ddd, *J*=3.6, 5.0, 8.9 Hz, CH_2), 1.29 (1H, ddd, *J*=2.7, 6.6, 9.1 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 192.4 (C=O), 163.3 (CH=*C*(SCH$_3$)$_2$), 133.0 (C), 121.7 (CH), 112.8 (*C*H=C(SCH$_3$)$_2$), 106.5 (CH), 104.4 (CH), 33.8 (NCH$_3$), 31.7 (CH), 20.2 (CH), 17.1 (CH$_2$), 16.7 (SCH$_3$), 14.8 (SCH$_3$); *m*/*z* 267 (10, M$^+$), 220 (50), 204 (60), 148 (100).

5.2.4. 3,3-Bis(methylthio)-1-[2-(2-furyl)cyclopropyl]-2-methyl-2-propen-1-one (7d). Yield (2.41 g, 90%) as a red viscous oil; [Found: C, 58.26; H, 6.11. $C_{13}H_{16}O_2S_2$ requires C, 58.17; H, 6.01%]; R_f (12% EtOAc/hexane) 0.48; ν_{max}(KBr) 2922, 1662 (C=O), 1550, 1429 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.24 (1H, d, *J*=1.7 Hz, HetAr), 6.27 (1H, dd, *J*=1.7, 2.9 Hz, HetAr), 6.08 (1H, d, *J*=2.9 Hz, HetAr), 2.58 (1H, ddd, *J*=4.2, 6.2, 9.4 Hz, C*H*–C=O), 2.51 (1H, ddd, *J*=4.2, 5.1, 9.0 Hz, C*H*–HetAr), 2.33 (3H, s, SCH$_3$), 2.20 (3H, s, SCH$_3$), 2.14 (3H, s, CH$_3$), 1.72 (1H, ddd, *J*=4.2, 5.3, 9.1 Hz, CH_2), 1.51 (1H, ddd, *J*=3.9, 6.8, 10.1 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 203.4 (C=O), 153.7 (C=*C*(SCH$_3$)$_2$), 144.2 (C), 140.7 (CH), 137.0 (*C*=C(SCH$_3$)$_2$), 111.0 (CH), 105.2 (CH), 30.5 (CH), 23.8 (CH), 19.5 (CH$_2$), 17.4 (SCH$_3$), 17.3 (SCH$_3$), 16.4 (CH$_3$); *m*/*z* 268 (20, M$^+$), 254 (100), 223 (86).

5.2.5. 3,3-Bis(methylthio)-2-methyl-1-[2-(5-methyl-2-furyl)cyclopropyl]-2-propen-1-one (7e). Yield (2.65 g, 94%) as a red viscous oil; [Found: C, 59.63; H, 6.36. $C_{14}H_{18}O_2S_2$ requires C, 59.54; H, 6.42%]; R_f (12% EtOAc/

hexane) 0.49; $\nu_{max}(CH_2Cl_2)$ 2925, 1671 (C=O), 1567, 1430 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.95 (1H, d, *J*=2.9 Hz, HetAr), 5.85 (1H, d, *J*=2.9 Hz, HetAr), 2.53 (1H, ddd, *J*=4.2, 6.6, 9.0 Hz, C*H*–C=O), 2.48 (1H, ddd, *J*=1.5, 5.6, 8.6 Hz, C*H*–HetAr), 2.33 (3H, s, SCH_3), 2.22 (6H, s, SCH_3, CH_3), 2.14 (3H, s, CH_3), 1.70 (1H, ddd, *J*=3.6, 5.4, 9.1 Hz, C*H*$_2$), 1.48 (1H, ddd, *J*=3.9, 6.6, 8.1 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 203.7 (C=O), 152.0 (C=*C*(SCH_3)$_2$), 150.5 (C), 144.5 (C), 136.6 (*C*=C(SCH_3)$_2$), 106.2 (CH), 106.0 (CH), 30.7 (CH), 24.1 (CH), 19.5 (CH_2), 17.5 (SCH_3), 17.4 (SCH_3), 16.5 (CH_3), 13.4 (CH_3); *m*/*z* 282 (26, M^+), 266 (85), 235 (100).

5.2.6. 3,3-Bis(methylthio)-2-methyl-1-[2-(2-thienyl)-cyclopropyl]-2-propen-1-one (7f). Yield (2.58 g, 91%) as a pale yellow viscous oil; [Found: 54.97; H, 5.71. $C_{13}H_{16}OS_3$ requires C, 54.89; H, 5.67%]; R_f (12% EtOAc/hexane) 0.44; $\nu_{max}(CH_2Cl_2)$ 2921, 1664 (C=O), 1544, 1428 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.05 (1H, d, *J*=5.1 Hz, HetAr), 6.89 (1H, t, *J*=4.2 Hz, HetAr), 6.82 (1H, d, *J*=3.4 Hz, HetAr), 2.76 (1H, ddd, *J*=4.2, 6.1, 9.4 Hz, C*H*–C=O), 2.41 (1H, ddd, *J*=4.4, 5.1, 7.6 Hz, C*H*–HetAr), 2.31 (3H, s, SCH_3), 2.19 (3H, s, SCH_3), 2.12 (3H, s, CH_3), 1.80 (1H, ddd, *J*=4.8, 5.1, 9.0 Hz, C*H*$_2$), 1.44 (1H, ddd, *J*=4.4, 7.1, 7.4 Hz, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 203.5 (C=O), 144.6 (C=*C*(SCH_3)$_2$), 144.3 (C), 137.0 (*C*=C(SCH_3)$_2$), 126.8 (CH), 123.8 (CH), 123.0 (CH), 33.9 (CH), 25.9 (CH), 20.6 (CH_2), 19.6 (SCH_3), 17.4 (SCH_3), 16.5 (CH_3); *m*/*z* 284 (37, M^+), 268 (100), 237 (40).

5.2.7. 3,3-Bis(methylthio)-2-methyl-1-[2-(1-*N*-methyl-2-pyrrolyl)cyclopropyl]-2-propen-1-one (7g). Yield (2.50 g, 89%) as a colourless solid, mp 83–84 °C; [Found: C, 59.67; H, 6.91; N, 5.09. $C_{14}H_{19}NOS_2$ requires C, 59.75; H, 6.80; N, 4.98%]; R_f (8% EtOAc/hexane) 0.21; ν_{max}(KBr) 2904, 1661 (C=O), 1561, 1420 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.56 (1H, t, *J*=2.2 Hz, HetAr), 6.00 (1H, t, *J*=3.2 Hz, HetAr), 5.80 (1H, dd, *J*=1.7, 3.6 Hz, HetAr), 3.62 (3H, s, NCH_3), 2.48 (1H, ddd, *J*=3.9, 5.9, 9.2 Hz, C*H*–C=O), 2.34 (3H, s, SCH_3), 2.32–2.29 (1H, m, C*H*–HetAr), 2.25 (3H, s, SCH_3), 2.16 (3H, s, CH_3), 1.70 (1H, ddd, *J*=3.9, 5.0, 8.8 Hz, C*H*$_2$), 1.42 (1H, ddd, *J*=3.9, 5.5, 8.9 Hz, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 204.2 (C=O), 144.6 (C=*C*(SCH_3)$_2$), 136.2 (C), 132.3 (*C*=C(SCH_3)$_2$), 122.0 (CH), 106.5 (CH), 104.7 (CH), 33.8 (NCH_3), 31.4 (CH), 22.1 (CH), 19.7 (CH_2), 18.4 (SCH_3), 17.5 (SCH_3), 16.5 (CH_3); *m*/*z* 281 (30, M^+), 279 (90, M^+-2H), 264 (70), 236 (100), 217 (70).

5.3. Procedure for $BF_3{\cdot}Et_2O$ induced rearrangement of cyclopropyl ketone 7a to 10a

To a solution of cyclopropyl ketone **7a** (0.25 g, 1 mmol) in C_6H_6 (15 mL), $BF_3{\cdot}Et_2O$ (0.19 mL, 1.5 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 12 h. It was then poured into cold saturated $NaHCO_3$ solution (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with H_2O (2×50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford crude viscous oil **10a** which was purified by column chromatography over silica gel using EtOAc/hexane (5:95) as eluent.

5.3.1. 2-Bis(methylthio)methylene-3-(2-furyl)-1-cyclopentanone (10a). Yield (0.19 g, 75%) as a red viscous oil; [Found: C, 56.59; H, 5.61. $C_{12}H_{14}O_2S_2$ requires C, 56.66; H, 5.55%]; R_f (20% EtOAc/hexane) 0.43; $\nu_{max}(CH_2Cl_2)$ 2982, 1684 (C=O), 1515, 1265 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33 (1H, d, *J*=2.0 Hz, HetAr), 6.27 (1H, dd, *J*=2.0, 3.2 Hz, HetAr), 5.95 (1H, d, *J*=2.7 Hz, HetAr), 4.52 (1H, t, *J*=4.6 Hz, C*H*–CH_2), 2.54–2.64 (1H, m, CO–C*H*$_2$), 2.51 (3H, s, SCH_3), 2.39–2.44 (1H, m, CO–C*H*$_2$), 2.36 (3H, s, SCH_3), 2.17–2.24 (2H, m, CH–C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 201.7 (C=O), 156.15 (C=*C*(SCH_3)$_2$), 154.0 (C), 141.56 (CH), 135.9 (*C*=C(SCH_3)$_2$), 110.1 (CH), 105.7 (CH), 44.0 (CH), 38.5 (CH_2), 26.4 (CH_2), 18.4 (SCH_3), 18.2 (SCH_3); *m*/*z* 254 (45, M^+), 207 (72), 191 (79).

5.4. Procedure for $SnCl_4$ induced rearrangement of cyclopropyl ketone 7b to 10b

To a solution of cyclopropyl ketone **7b** (1 mmol) in CH_3NO_2 (15 mL), $SnCl_4$ (0.18 mL, 1.5 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 12 h (monitored by TLC). The mixture was then poured into cold saturated $NaHCO_3$ solution (25 mL), extracted with CH_2Cl_2 (3×15 mL) and the organic extracts were washed with H_2O (2×50 mL), brine (50 mL) and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford crude residue which was purified by column chromatography over silica gel using EtOAc/hexane as eluent.

5.4.1. 2-Bis(methylthio)methylene-3-(2-thienyl)-1-cyclopentanone (10b). Yield (0.19 g, 72%) as a red viscous oil; [Found: C, 53.36; H, 5.29. $C_{12}H_{14}OS_3$ requires C, 53.30; H, 5.22%]; R_f (20% EtOAc/hexane) 0.41; $\nu_{max}(CH_2Cl_2)$ 2923, 1686 (C=O), 1512 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.16 (1H, dd, *J*=1.0, 5.1 Hz, HetAr), 6.91 (1H, dd, *J*=3.6, 5.0 Hz, HetAr), 6.77 (1H, dd, *J*=1.0, 3.6 Hz, HetAr), 4.74 (1H, brd, *J*=7.1 Hz, C*H*–CH_2), 2.55–2.67 (1H, m, CH–C*H*$_2$), 2.52 (3H, s, SCH_3), 2.36 (3H, s, SCH_3), 2.31–2.40 (2H, m, CO–C*H*$_2$–C*H*$_2$), 2.08–2.13 (1H, m, CH–C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 201.4 (C=O), 154.5 (C=*C*(SCH_3)$_2$), 148.0 (C), 137.9 (*C*=C(SCH_3)$_2$), 126.7 (CH), 124.0 (CH), 123.6 (CH), 45.4 (CH), 38.3 (CH_2), 30.2 (CH_2), 18.6 (SCH_3), 18.2 (SCH_3); *m*/*z* 270 (30, M^+), 221 (100), 172 (52).

5.5. Procedure for Amberlyst-15 resin induced rearrangement of cyclopropyl ketone 7c to 10c

To a solution of cyclopropyl ketone **7c** (0.26 g, 1 mmol) in CH_2Cl_2 (10 mL), Amberlyst-15 resin (1.5 g) was added and the reaction mixture was stirred at room temperature for 48 h. The mixture was then filtered through celite, washed with CH_2Cl_2 (3×15 mL), the filtrate evaporated under reduced pressure to afford crude residue which was purified by column chromatography over silica gel using EtOAc/hexane (1:9) as eluent.

5.5.1. 2-Bis(methylthio)methylene-3-(1-*N*-methyl-2-pyrrolyl)-1-cyclopentanone (10c). Yield (0.12 g, 43%) as a yellow viscous oil; [Found: C, 56.59; H, 5.61. $C_{13}H_{17}NOS_2$ requires C, 58.39; H, 6.41; N, 5.24%]; R_f (25% EtOAc/hexane) 0.42; $\nu_{max}(CH_2Cl_2)$ 2925, 1684 (C=O), 1514 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.57 (1H, dd,

J=1.2, 1.8 Hz, HetAr), 5.98 (1H, dd, J=1.9, 2.2 Hz, HetAr), 5.63 (1H, dd, J=1.2, 2.3 Hz, HetAr), 4.44 (1H, brd, J=5 Hz, CH–CH_2), 3.66 (3H, s, NCH_3), 2.51–2.54 (1H, m, CO–CH_2), 2.50 (3H, s, SCH_3), 2.31–2.36 (1H, m, CO–CH_2), 2.30 (3H, s, SCH_3), 2.24–2.28 (1H, m, CH–CH_2), 1.89–1.91 (1H, m, CH–CH_2); δ_C (100 MHz, $CDCl_3$) 201.8 (C=O), 153.4 (C=C(SCH_3)$_2$), 137.5 (C), 134.6 (C=C(SCH_3)$_2$), 121.6 (CH), 106.5 (CH), 105.8 (CH), 42.1 (CH), 38.0 (NCH_3), 33.73 (CH_2), 27.2 (CH_2), 18.5 (SCH_3), 18.0 (SCH_3); m/z 267 (50, M^+), 220 (90), 204 (100).

5.6. Procedure for acid induced rearrangements of cyclopropyl ketones 7d–e

(a) With $SnCl_4$. General procedure described for cyclopropyl ketone **7b** was followed.

Cyclization of **7d** afforded **11d** and **12d** (Table 2).

The product **11d** was found to be an inseparable mixture of two diastereomers.

5.6.1. *S*-Methyl *t*-2-(2-furyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate and *S*-methyl *c*-2-(2-furyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate (11d). (2.4:1) Total yield (0.16 g, 65%) as a pale yellow viscous oil; [Found: C, 60.57; H, 5.89. $C_{12}H_{14}O_3S$ requires C, 60.48; H, 5.92%]; R_f (10% EtOAc/hexane) 0.22; ν_{max}(CH_2Cl_2) 3116, 2971, 1745 (C=O), 1665 (C(=O)SCH_3) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [7.36 (1H, d, J=1.9 Hz, HetAr)] 7.34 (1H, d, J=2.0 Hz, HetAr), 6.31 (1H, dd, J=2.0, 3.2 Hz, HetAr) [6.29 (1H, dd, J=2.1, 3.2 Hz, HetAr)], 6.14 (1H, d, J=3.2 Hz, HetAr) [6.10 (1H, d, J=3.1 Hz, HetAr)], 4.20 (1H, dd, J=6.8, 10.3 Hz, CH–CH_2) [3.30 (1H, dd, J=6.6, 12.2 Hz, CH–CH_2)], [2.59–2.71 (2H, m, CO–CH_2)] 2.42–2.58 (2H, m, CO–CH_2), [2.39–2.41 (1H, m, CH–CH_2)] 2.34–2.38 (1H, m, CH–CH_2), 2.34 (3H, s, SCH_3), [2.29–2.32 (1H, m, CH–CH_2)] 2.12–2.19 (1H, m, CH–CH_2), [2.08 (3H, s, SCH_3)], [1.59 (3H, s, CH_3)] 1.12 (3H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) [215.3] 213.7 (C=O), [200.1]200.0 (C(=O)SCH_3), 153.4[152.6] (C), 142.1[141.9] (CH), [110.3]110.0 (CH), 107.2[106.7] (CH), 67.3[66.5] (C–C(=O)SCH_3), [48.4]44.0 (CH), 37.4[37.3] (CH_2), [23.7]23.2 (CH_2), [18.4]15.4 (SCH_3), [12.1]11.1 (CH_3); m/z 238 (15, M^+), 163 (100).

5.6.2. 3,3-Bis(methylthio)-1-(cyclopenta[*b*]furan-4-yl)-2-methyl-2-propen-1-one (12d). Yield (0.16 g, 58%) as a pale yellow viscous oil; [Found: C, 58.29; H, 6.09. $C_{13}H_{16}O_2S_2$ requires C, 58.17; H, 6.01%]; R_f (10% EtOAc/hexane) 0.21; ν_{max}(CH_2Cl_2) 3125, 2924, 1681 (C=O), 1590, 1435 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34 (1H, d, J=2 Hz, HetAr), 6.69 (1H, d, J=2 Hz, HetAr), 5.07 (1H, dd, J=5.9, 10.2 Hz, CH–CH_2–CH_2), 2.57–2.62 (2H, m, CH–CH_2–CH_2), 2.34 (3H, s, SCH_3), 2.32 (3H, s, SCH_3), 2.08–2.15 (2H, m, CH–CH_2–CH_2), 1.85 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 194.1 (C=O), 167.1 (C=C(SCH_3)$_2$), 143.0 (C), 142.3 (CH), 131.9 (C=C(SCH_3)$_2$), 121.7 (C), 106.5 (CH), 41.7 (CH), 37.6 (CH_2), 28.3 (CH_2), 18.4 (SCH_3), 17.7 (SCH_3), 16.8 (CH_3); m/z 268 (88, M^+), 206 (52), 204(100).

Cyclization of **7e** gave products **11e** and **12e** (Table 2).

The product **11e** was found to be an inseparable mixture of two diastereomers.

5.6.3. *S*-Methyl *t*-2-(5-methyl-2-furyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate and *S*-methyl *c*-2-(5-methyl-2-furyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate (11e). (3:1) Total yield (0.06 g, 25%) as a pale yellow viscous oil; [Found: C, 61.94; H, 6.25. $C_{13}H_{16}O_3S$ requires C, 61.88; H, 6.39%]; R_f (10% EtOAc/hexane) 0.30; ν_{max}(CH_2Cl_2) 2929, 1744 (C=O), 1664 (C(=O)SCH_3), 1429 cm^{-1}; [methyl *c*-2-(5-methyl-2-furyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate exists as a minor isomer, δ value is given inside bracket and (1:3) ratio was determined by NMR] δ_H (400 MHz, $CDCl_3$) 5.99 (1H, d, J=2.9 Hz, HetAr) [5.97 (1H, d, J=2.9 Hz, HetAr)], [5.89 (1H, d, J=2.9 Hz, HetAr)] 5.87 (1H, d, J=2.9 Hz, HetAr), 4.12 (1H, dd, J=6.8, 10.0 Hz, CH–CH_2) [3.12 (1H, dd, J=6.8, 11.0 Hz, CH–CH_2)], 2.52–2.63 (2H, m, CO–CH_2) [2.37–2.39 (2H, m, CO–CH_2)], 2.35 (3H, s, SCH_3), 2.33–2.34 (1H, m, CH–CH_2), [2.32 (3H, s, SCH_3)] 2.25–2.28 (1H, m, CH–CH_2), 2.23 (3H, s, CH_3) [2.22 (3H, s, CH_3)], [2.21–2.23 (1H, m, CH–CH_2)] 2.07–2.18 (1H, m, CH–CH_2), [1.17 (3H, s, CH_3)] 1.14 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) [214.4]214.0 (C=O), 200.2[200.0] (C(=O)SCH_3), 151.6[151.4] (C), 151.3[151.1] (C), 107.9[107.5] (CH), [105.9]105.8 (CH), 67.3[66.1] (C–C(=O)SCH_3), [49.9]44.22 (CH), 37.4[34.8] (CH_2), [25.2]23.3 (CH_2), [20.3]15.4 (SCH_3), [14.8]13.5 (CH_3), [14.2]12.0 (CH_3); m/z 252 (15, M^+), 163 (100).

5.6.4. 3,3-Bis(methylthio)-1-(2-methyl-cyclopenta[*b*]-furan-4-yl)-2-methyl-2-propen-1-one (12e). Yield (0.20 g, 69%) as a pale yellow viscous oil; [Found: C, 59.62; H, 6.34. $C_{14}H_{18}O_2S_2$ requires C, 59.54; H, 6.42%]; R_f (12% EtOAc/hexane) 0.20; ν_{max}(CH_2Cl_2) 3116, 2921, 1677 (C=O), 1574, 1429 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.26 (1H, s, HetAr), 5.00 (1H, dd, J=5.6, 10.1 Hz, CH–CH_2–CH_2), 2.49–2.57 (2H, m, CH–CH_2–CH_2), 2.34 (3H, s, SCH_3), 2.32 (3H, s, SCH_3), 2.28 (3H, s, CH_3), 2.02–2.14 (2H, m, CH–CH_2–CH_2), 1.86 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 194.1 (C=O), 165.9 (C=C(SCH_3)$_2$), 153.1 (C), 142.9 (C), 131.4 (C=C(SCH_3)$_2$), 122.7 (C), 102.0 (CH), 41.6 (CH), 37.4 (CH_2), 28.4 (CH_2), 18.4 (SCH_3), 17.7 (SCH_3), 16.8 (CH_3), 13.4 (CH_3); m/z 282 (16, M^+), 220 (75), 218 (87).

(b) With TFA. To a solution of cyclopropyl ketones **7d–e** (1 mmol) in CH_2Cl_2 (15 mL), TFA (0.12 mL, 1.5 mmol) was added dropwise at 0 °C and the reaction mixture were stirred at room temperature for 12–14 h (monitored by TLC). It was then poured into cold saturated $NaHCO_3$ solution (25 mL), extracted with CH_2Cl_2 (3×15 mL), the combined organic extracts were washed with H_2O (2×50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford crude products, which were purified by column chromatography over silica gel using EtOAc/hexane as eluent.

Cyclization of **7d–e** gave products **11d–e** and **12d–e** (Table 2).

5.7. $HgCl_2$ induced hydrolysis of 12d–e

To a solution of either **12d** or **12e** (0.5 mmol) in CH_3CN/

H_2O (3:1) (10 mL), was added $HgCl_2$ (0.271 g, 1 mmol) and the reaction mixture was refluxed with stirring for 12–24 h (monitored by TLC). It was then cooled, filtered through celite and the filtrated was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL), washed with H_2O (2×25 mL), brine (25 mL), dried (Na_2SO_4) and was evaporated under reduced pressure to give crude **13d–e** which were purified by column chromatography over silica gel using EtOAc/hexane (5:95) as eluent.

5.7.1. Methyl 3-(cyclopenta[*b*]furan-4-yl)-2-methyl-3-oxo-propane carbothioate (13d). Yield (0.08 g, 70%) as a pale yellow viscous oil; [Found: C, 60.55; H, 5.99. $C_{12}H_{14}O_3S$ requires C, 60.48; H, 5.92%]; R_f (12% EtOAc/hexane) 0.15; $\nu_{max}(CH_2Cl_2)$ 3124, 2934, 1681 (C═O), 1675 (C(═O)SCH_3), 1589, 1448 cm^{-1}; [**13d** exists as a mixture of diastereomers and 1:1.3 ratio was determined by NMR. δ value of minor diastereomer is given inside bracket] δ_H (400 MHz, $CDCl_3$) [7.36 (1H, d, J=2.2 Hz, HetAr)] 7.34 (1H, d, J=2.2 Hz, HetAr), [6.69(1H, d, J=2.2 Hz, HetAr)] 6.68 (1H, d, J=2.2 Hz, HetAr), 3.52–3.56 (1H, m, C*H*–CH_3) [3.35–3.40 (1H, m, C*H*–CH_3)], 3.29 (1H, ddd, J=13.0, 7.1, 7.0 Hz, C*H*–CH_2–CH_2) [3.09 (1H, ddd, J=14.9, 7.1, 6.8 Hz, C*H*–CH_2–CH_2)], 2.63–2.66 (1H, m, CH–CH_2–C*H*$_2$) [2.57–2.62 (1H, m, CH–CH_2–C*H*$_2$)], 2.47–2.52 (1H, m, CH–CH_2–C*H*$_2$) [2.43–2.46 (1H, m, CH–CH_2–C*H*$_2$)], 2.35 (3H, s, SCH_3) [2.33 (3H, s, SCH_3)], 2.18–2.25 (1H, m, CH–C*H*$_2$–CH_2) [2.16–2.17 (1H, m, CH–C*H*$_2$–CH_2)], 2.01–2.07 (1H, m, CH–C*H*$_2$–CH_2) [1.96–2.00 (1H, m, CH–C*H*$_2$–CH_2)], [1.35 (3H, d, J=6.8 Hz, CH–C*H*$_3$)] 1.21 (3H, d, J=7.1 Hz, 3H; CH–C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 201.8[201.8] (C═O), 193.9[193.7] (C(═O)SCH_3), [167.1]166.6 (C), [143.1]143.0 (CH), 121.7[121.6] (C), [106.8]106.6 (CH), [49.7]48.7 (CH), [37.4]37.3 (CH), 37.2[35.8] (CH_2), [26.7]24.9 (CH_2), [16.3]13.6 (SCH_3), 11.7[11.6] (CH_3); *m*/*z* 238 (15, M^+), 163 (100).

5.7.2. Methyl 2-methyl-3-(2-methyl-cyclopenta[*b*]furan-4yl)-3-oxo-propane carbothioate (13e). Yield (0.10 g, 80%) as a pale red viscous oil; [Found: C, 61.97; H, 6.42. $C_{13}H_{16}O_3S$ requires C, 61.88; H, 6.39%]; R_f (10% EtOAc/hexane) 0.12; $\nu_{max}(CH_2Cl_2)$ 3119, 2933, 1679 (C═O), 1672 (C(═O)SCH_3), 1575, 1435 cm^{-1}; [**13e** exists as a mixture of diastereomers and 1:3 ratio was determined by NMR. δ value of minor diastereomer is given inside bracket] δ_H (400 MHz, $CDCl_3$) 6.25 (1H, s, HetAr) [6.24 (1H, s, HetAr)], [3.50–3.46 (1H, m, C*H*–CH_3)] 3.31–3.28 (1H, m, C*H*–CH_3), 3.29 (1H, m, C*H*–CH_2–CH_2) [3.08 (1H, ddd, J=14.9, 7.4, 7.1 Hz, C*H*–CH_2–CH_2)], 2.58–2.62 (1H, m, CH–CH_2–C*H*$_2$) [2.52–2.57 (1H, m, CH–CH_2–C*H*$_2$)], 2.44–2.48 (1H, m, CH–CH_2–C*H*$_2$) [2.38–2.43 (1H, m, CH–CH_2–C*H*$_2$)], [2.35 (3H, s, SCH_3)] 2.32 (3H, s, SCH_3), 2.30 (3H, s, CH_3) [2.28 (3H, s, CH_3)], 2.18–2.25 (1H, m, CH–C*H*$_2$–CH_2) [2.16–2.17 (1H, m, CH–C*H*$_2$–CH_2)], 2.01–2.07 (1H, m, CH–C*H*$_2$–CH_2) [1.96–2.00 (1H, m, CH–C*H*$_2$–CH_2)], 1.35 (3H, d, J=6.8 Hz, CH–C*H*$_3$) [1.20 (3H, d, J=7.1 Hz, CH–C*H*$_3$)]; δ_C (100 MHz, $CDCl_3$) 202.1[202.0] (C═O), 194.2[194.1] (C(═O)SCH_3), 165.9[165.4] (C), 153.23[153.16] (C), [122.6]122.4 (C), [120.5]120.1 (CH), 49.7[48.8] (CH), 37.4[37.3] (CH), [37.0]35.5 (CH_2), 26.7[24.8] (CH_2), 16.6[16.4] (SCH_3), 13.5[13.45] (CH_3), [13.4]11.72 (CH_3); *m*/*z* 252 (15, M^+), 176 (53), 149 (100).

5.8. Procedure for acid induced rearrangements of cyclopropyl ketone 7f

(a) With $SnCl_4$. General procedure described for cyclopropyl ketones **7b** was followed.

Cyclization of 2-(2-thienyl) cyclopropyl ketone **7f** gave products **11f**, **12f** and **8f** (Table 3).

The product **11f** was found to be an inseparable mixture of two diastereomers.

5.8.1. *S*-Methyl *t*-2-(2-thienyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate and *S*-methyl *c*-2-(2-thienyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate (11f). (4:1) Total yield (0.17 g, 65%) as a pale yellow viscous oil; [Found: C, 56.72; H, 5.62. $C_{12}H_{14}O_2S_2$ requires C, 56.66; H, 5.55%]; R_f (10% EtOAc/hexane) 0.20; $\nu_{max}(CH_2Cl_2)$ 3060, 2975, 1744 (C═O), 1665 (C(═O)SCH_3), 1447 cm^{-1}; [methyl *c*-2-(2-thienyl)-1-methyl-5-oxo-cyclopentane-*r*-1-carbothioate exists as a minor isomer, δ value is given inside bracket and (1:4) ratio was determined by NMR] δ_H (400 MHz, $CDCl_3$) [7.21–7.22 (1H, m, HetAr)] 7.19 (1H, dd, J=1.0, 5.2 Hz, HetAr), [6.98–6.99 (1H, m, HetAr)] 6.97 (1H, dd, J=2.0, 5.1 Hz, HetAr), [6.89–6.90 (1H, m, HetAr)]6.85 (1H, dd, J=1.0, 2.3 Hz, HetAr), 4.45 (1H, dd, J=6.4, 11.7 Hz, C*H*–CH_2) [4.41 (1H, dd, J=6.4, 11.0 Hz, C*H*–CH_2)], [2.52–2.54 (2H, m, CO–C*H*$_2$)] 2.41–2.50 (2H, m, CO–C*H*$_2$), [2.38–2.40 (1H, m, CH–C*H*$_2$)] 2.35–2.37 (1H, m, CH–C*H*$_2$), 2.33 (3H, s, SCH_3), [2.20–2.29 (1H, m, CH–C*H*$_2$)] 2.12–2.17 (1H, m, CH–C*H*$_2$), [2.03 (3H, s, SCH_3)], [1.16 (3H, s, CH_3)] 1.08 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 213.1[203.6] (C═O), 200.1[196.6] (C(═O)SCH_3), [146.2]141.2 (C), 126.6[126.1] (CH), [125.2]125.1 (CH), [124.5]124.1 (CH), 67.6[61.2] (*C*–C(═O)SCH_3), [45.4]44.9 (CH), [38.8]37.6 (CH_2), [30.1]25.4 (CH_2), 14.6[13.8] (SCH_3), 11.9[11.7] (CH_3); *m*/*z* 254 (15, M^+), 206 (80), 178 (100).

5.8.2. 3,3-Bis(methylthio)-1-(cyclopenta[*b*]thiophen-4-yl)-2-methyl-2-propen-1-one (12f). Yield (0.17 g, 61%) as a pale yellow viscous oil; [Found: C, 54.96; 5.59. $C_{13}H_{16}OS_3$ requires C, 54.89; H, 5.67%]; R_f (10% EtOAc/hexane) 0.25; $\nu_{max}(CH_2Cl_2)$ 3085, 2920, 1672 (C═O), 1516, 1404 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, J=5.2 Hz, HetAr), 7.09 (1H, d, J=5.2 Hz, HetAr), 5.21 (1H, dd, J=4.6, 11.0 Hz, C*H*–CH_2–CH_2), 2.57–2.74 (2H, m, CH–CH_2–C*H*$_2$), 2.37 (3H, s, SCH_3), 2.33 (3H, s, SCH_3), 2.22–2.27 (1H, m, CH–C*H*$_2$–CH_2), 2.09–2.17 (1H, m, CH–C*H*$_2$–CH_2), 1.94 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 192.6 (C═O), 159.0 (C═*C*(SCH_3)$_2$), 144.3 (C), 137.0 (C), 132.2 (*C*═C(SCH_3)$_2$), 125.1 (CH), 123.8 (CH), 43.9 (CH), 38.0 (CH_2), 29.4 (CH_2), 18.3 (SCH_3), 18.0 (SCH_3), 16.8 (CH_3); *m*/*z* 284 (50 M^+), 220 (100).

5.8.3. 4a-Methyl-4,4-bis(methylthio)-4,4a,5,6,7,7a-hexahydropentaleno[1,2-*b*]thiophen-5-one (8f). Yield (0.03 g, 10%) as a pale yellow viscous oil; [Found: C, 54.81; 5.73. $C_{13}H_{16}OS_3$ requires C, 54.89; H, 5.67%]; R_f (10% EtOAc/hexane) 0.30; $\nu_{max}(CH_2Cl_2)$ 3107, 2978, 1740 (C═O),

1671 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (1H, d, J=5.1 Hz, HetAr), 6.83 (1H, d, J=5.1 Hz, HetAr), 3.67 (1H, dd, J=2.9, 6.5 Hz, C*H*–CH_2), 2.32–2.37 (2H, m, CO–C*H*$_2$), 2.25 (3H, s, SCH_3), 2.10–2.21 (2H, m, CH–C*H*$_2$), 2.04 (3H, s, SCH_3), 1.42 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 216.5 (C=O), 147.8 (C), 143.6 (C), 128.8 (CH), 121.7 (CH), 70.5 (C), 67.8 (C), 51.9 (CH), 38.6 (CH_2), 25.1 (CH_2), 20.5 (SCH_3), 14.2 (SCH_3), 13.7 (CH_3); *m/z* 284 (30, M^+), 237 (100).

(b) In TFA. Procedure described in cyclopropyl ketones **7d–e** was followed.

Cyclization of **7f** gave products **12f** (Table 3, entry 3).

(c) In H_3PO_4. A solution of cyclopropyl ketone **7f** (1 mmol) in H_3PO_4 (88%, 10 mL) was stirred either at room temperature or heated with stirring at 60 °C for 4–12 h (Table 3, entries 4 and 5). The reaction mixture was poured over cold saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was washed with H_2O (2×50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford crude product mixture, which was separated by column chromatography over silica gel using EtOAc/hexane as eluent.

Cyclization of **7f** gave products **12f** and **14f** (Table 3).

5.8.4. Methyl 2-benzo[*b*]thiophene-4-yl-propane carbothioate (14f). Yield (0.05 g, 20%) as a pale yellow viscous oil; [Found: C, 61.06; H, 5.24. $C_{12}H_{12}OS_2$ requires C, 60.98; H, 5.12%]; R_f (12% EtOAc/hexane) 0.48; $\nu_{max}(CH_2Cl_2)$ 2980, 2931, 1685 (C(=O)–SCH_3), 1452 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (1H, dd, J=2.8, 5.6 Hz, HetArH), 7.47–7.50 (2H, m, HetArH), 7.34–7.35 (1H, m, HetArH), 7.33 (1H, d, J=2.8 Hz, HetArH), 4.41 (1H, q, J=6.8 Hz, C*H*–CH_3), 2.23 (3H, s, SCH_3), 1.66 (3H, d, J=6.8 Hz, CH–C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 201.4 (C(=O)–SCH_3), 140.3 (C), 138.3 (C), 134.6 (C), 126.7 (CH), 124.5 (CH), 123.0 (CH), 121.8 (CH), 121.5 (CH), 51.83 (CH), 17.9 (SCH_3), 11.8 (CH_3); *m/z* 236 (10, M^+), 161 (60), 134 (50), 75 (100).

5.9. Procedure for acid induced rearrangements of cyclopropyl ketone 7g

(a) In TFA. Procedure described in cyclopropyl ketones **7d–e** was followed.

Cyclization of **7g** gave indole **15g**.

5.9.1. 1-*N*-Methyl-4-[1-methyl-2,2-bis(methylthio)vinyl]-indole (15g). Yield (0.18 g, 68%) as a pale yellow viscous oil; [Found: C, 63.91; H, 6.45; N, 5.41. $C_{14}H_{17}NS_2$ requires C, 63.83; H, 6.50; N, 5.32%]; R_f (8% EtOAc/hexane) 0.34; $\nu_{max}(CH_2Cl_2)$ 2984, 2918, 1577, 1425 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.27 (2H, m, HetArH), 7.00 (1H, d, J=3.0 Hz, HetArH), 6.86 (1H, dd, J=1.2, 6.8 Hz, HetArH), 6.30 (1H, d, J=3.0 Hz, HetArH), 3.79 (3H, s, NCH_3), 2.41 (3H, s, SCH_3), 2.40 (3H, s, SCH_3), 2.11 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 144.5 (C=*C*(SCH_3)$_2$), 136.7 (C), 136.6 (C), 129.7 (C), 128.7 (CH), 126.0 (*C*=C(SCH_3)$_2$), 121.3 (CH), 118.0 (CH), 108.1 (CH), 100.0 (CH), 33.0 (CH_3), 24.3 (CH_3), 17.7 (SCH_3), 17.2 (SCH_3); *m/z* 263 (90, M^+), 201 (100), 168 (88).

(b) In PTSA. To a solution of (2-pyrrolyl) cyclopropyl ketone **7g** (0.28 g, 1 mmol) in C_6H_6 (15 mL), PTSA·H_2O (0.22 g, 1.1 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. It was then poured into cold saturated $NaHCO_3$ solution (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with H_2O (2×50 mL), brine (50 mL) and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure to afford crude viscous oil which was purified by column chromatography over silica gel using EtOAc/hexane as eluent (2:98) to give **14g** (35%) and **15g** (40%).

5.9.2. Methyl 2-(1-*N*-methyl-4-indolyl)propane carbothioate (14g). Yield (0.08 g, 35%) as a pale yellow viscous oil; [Found: C, 66.99; H, 6.42; N, 6.09. $C_{13}H_{15}NOS$ requires C, 66.92; H, 6.48; N, 6.00.]; R_f (8% EtOAc/hexane) 0.25; $\nu_{max}(CH_2Cl_2)$ 2980, 1684 (C(=O)–SCH_3), 1444 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.28 (2H, m, HetArH), 7.09–7.10 (1H, m, HetArH), 7.08 (1H, d, J=3.2 Hz, HetArH), 6.57 (1H, d, J=3.2 Hz, HetArH), 4.32 (1H, q, J=7.3 Hz, C*H*–CH_3), 3.78 (3H, s, NCH_3), 2.21 (3H, s, SCH_3), 1.66 (3H, d, J=7.3 Hz, CH–C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 201.8 (C(=O)–SCH_3), 136.7 (C), 131.8 (C), 128.9 (CH), 127.4 (C), 121.8 (CH), 118.2 (CH), 108.6 (CH), 99.2 (CH), 51.8 (CH), 33.0 (CH_3), 17.5 (SCH_3), 11.8 (CH_3); *m/z* 233 (15, M^+), 158 (100), 143 (80), 75 (92).

5.9.3. BF_3·Et_2O catalyzed methanolysis of 15g. A suspension of **15g** (0.13 g, 0.5 mmol) and $HgCl_2$ (1.36 g, 5 mmol) in dry MeOH (5 mL) was stirred at room temperature (10 min) followed by addition of BF_3·Et_2O (0.5 mL, 3.9 mmol). The reaction mixture was refluxed (0.5 h), cooled and filtered to remove mercury salts. The filtrate was poured into saturated $NaHCO_3$ solution (25 mL), extracted with Et_2O (3×10 mL). The combined organic extract was washed with H_2O (2×25 mL), brine (25 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford crude yellow oil which was passed through silica gel column using EtOAc/hexane (2:98) as eluent to give **16g**.

5.9.4. Methyl 2-(1-*N*-methyl-4-indolyl)propanoate (16g). Yield (0.09 g, 85%) as a pale yellow viscous oil; [Found: C, 71.93; H, 6.86; N, 6.52. $C_{13}H_{15}NO_2$ requires C, 71.86; H, 6.96; N, 6.45%]; R_f (8% EtOAc/hexane) 0.19; $\nu_{max}(CH_2Cl_2)$ 2983, 2946, 1730 (C(=O)–OCH_3), 1444 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.17–7.23 (2H, m, HetArH), 7.02–7.04 (2H, m, HetArH), 6.55 (1H, d, J=3.2 Hz, HetArH), 4.13 (1H, q, J=7.1 Hz, C*H*–CH_3), 3.74 (3H, s, OCH_3), 3.62 (3H, s, NCH_3), 1.61 (3H, d, J=7.1 Hz, CH–C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 175.3 (C(=O)–OCH_3), 136.7 (C), 132.7 (C), 128.7 (CH), 127.0 (C), 121.7 (CH), 117.4 (CH), 108.2 (CH), 99.0 (CH), 51.9 (OCH_3), 43.1 (CH) 32.8 (CH_3), 17.8 (CH_3); *m/z* 217 (80, M^+), 158 (100), 143 (85), 58 (90).

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A double alkylation—ring closing metathesis approach to spiroimines

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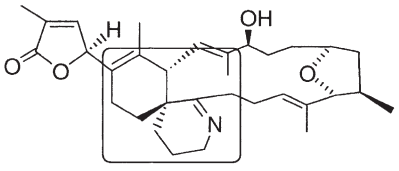
Abstract—As part of a programme directed towards the synthesis of the marine toxins, the spirolides and gymnodimine, a convenient synthesis of the key bicyclic spiroimine ring systems has been developed. The method involves double alkylation of a simple lactam, Grubbs ring closing metathesis of the resultant dialkylated lactam then reduction of the lactam to an imine.

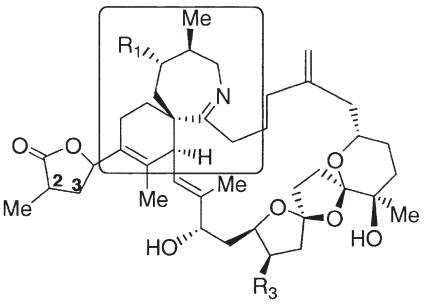
1. Introduction

Several shellfish toxins[1] formed during algal blooms contain spiroimine units as a key structural feature. Gymnodimine[2] (**1**) is a biotoxin isolated from New Zealand oysters (*Tiostrea chilensis*) that exhibits neurotoxic effects in a mouse bioassay and contains an azaspiro[5.5]undecadiene subunit. This 6,6-spirocyclic ring system is also present in the fast acting toxin spirocentrimine[3] isolated from a Taiwanese laboratory-cultured *Procentrum* species.



Gymnodimine **1**

The homologous azaspiro[5.6]dodecadiene ring system is a key structural feature of the macrocyclic toxins, spirolides A–D (**2**-**5**), isolated from the digestive glands of contaminated mussels (*Mytilus edulis*), scallops (*Placopecten magellanicus*) and toxic plankton from the eastern coast of Nova Scotia, Canada. Initially the structures of spirolides B (**3**) and D (**5**) were elucidated[4] together with spirolides E and F[5] that lacked the spiroimine unit. More recently, isolation and culture of a toxic clone of the dinoflagellate *Alexandrium ostenfeldii*, obtained from the same aquaculture site, allowed structural elucidation of spirolides A (**2**) and C (**3**).[6,7] The spirolides activate L-type calcium channels and act as muscarinic acetylcholine receptor antagonists. The key 7,6-spirocyclic imine pharmacophore present in the spirolides is also found in the related shellfish toxins, the pinnatoxins[8,9] and pteriatoxin.[10]



Spirolide A **2**; $\Delta_{2,3}$, R_1=H, R_2=Me
Spirolide B **3**; R_1=H, R_2=Me
Spirolide C **4**; $\Delta_{2,3}$, R_1=Me, R_2=Me
Spirolide D **5**; R_1=Me, R_2=Me

Gymnodamine in which the imine moiety is reduced, resulted in a significant decrease in toxicity[11] and the keto amine hydrolysis products of spirolides A–D, namely spirolides E and F, are also inactive[5] suggesting that the spiroimine portion of these shellfish toxins is the active

Keywords: Gymnodimi; Spirolactams; β-Trimethylsilylethoxycarbonyl (TEOC).
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pharmacophore. The mechanism of action of these imine-containing toxins was initially thought to involve covalent bond formation via nucleophilic addition to the imine, however Romo et al.[12] postulate that these α-quaternary substituted imines may serve as latent nucleophiles as a result of their masked enamine character as evidenced by their ability to completely incorporate deuterium at the exocyclic carbon after prolonged exposure to CD_3OD.

Diels–Alder cycloaddition of dienes to α-methylene lactams has provided an efficient method for the construction of the spirocyclic imine unit in gymnodimine[13,14] and pinnatoxin A.[15] White et al.[16] also recently reported a synthesis of the spiroimine unit of gymnodimine (**1**) via elaboration of a Diels–Alder adduct formed using an α-methylene derivative of Meldrum's acid as the dienophile. Other approaches to the spirocyclic imine unit in pinnatoxin A include the use of an aza-Wittig reaction of an azidoketone[17] and thermolysis of an aminoketone.[18] Prompted by the interesting architecture and biological activity of these spirocyclic imines present in these highly toxic shellfish toxins, we directed our attention to the synthesis of a range of spirocyclic imines as potential pharmacological probes. We therefore, herein report the full details[19] of an efficient synthesis of spirocyclic imines from simple lactams via double alkylation to generate a diene precursor followed by Grubbs' ring closing metathesis and reduction of the lactam to an imine (Scheme 1).

2. Results and discussion

Our initial attention focused on the synthesis of the parent spiroimine ring systems present in gymnodimine (**1**) and the spirolides (**2**-**5**) with the idea that nucleophilic addition of an organometallic species to the imine carbon[20] followed by reformation of the imine[21] from the resultant substituted amine would provide the methodology to access the substituted imine units present in the natural products. Our work was prompted by the use of an analogous double alkylation—ring closing metathesis strategy to construct bicyclic lactam peptidomimetics[22] and enantiopure spirocycles.[23]

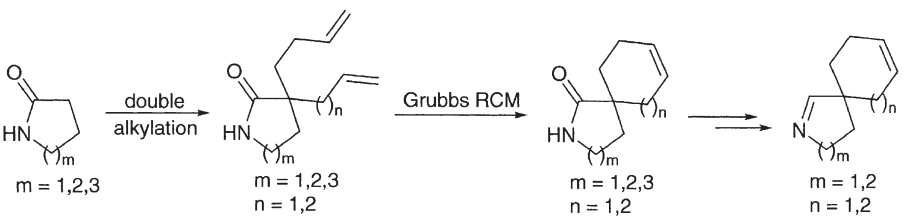
Initial attention focused on the lactam double α-alkylation step that required considerable experimentation to ascertain the optimum procedure. In analogous alkylation steps, lactams are often protected as *tert*-butoxycarbamates[22] or *N*-benzyl derivatives.[24,25] These bulky groups hindered the second alkylation step and base induced ring opening proved problematic when using a seven membered acylated lactam. In search of a general method for effecting an efficient double alkylation procedure we focused on the use of *N*-trimethylsilyl lactam derivatives. Covey et al.[26] have used *N*-trimethylsilyl lactams for the synthesis of α,α-dialkyl-ε-caprolactams however in their case the *N*-trimethylsilyl lactams were prepared in a separate step in benzene using triethylamine and trimethylsilyl chloride.

In the present work the *N*-trimethylsilyl lactams were prepared by treatment of the parent lactam with butyllithium in THF at −78 °C followed by quenching with trimethylsilyl chloride. The first α-alkylation step was then carried out directly without isolation and purification of the *N*-trimethylsilyl lactam. Five, six and seven membered lactams were doubly alkylated following similar conditions to that reported by Meyers et al.[27,28] (LDA, THF, −78 °C) thus providing the dialkylated dienes (**6**-**11**) listed in Table 1. In the case of the unsymmetrically disubstituted dienes (**6**), (**8**) and (**10**) the alkylation steps were performed sequentially whereas in the case of the symmetrically substituted dienes (**7**), (**9**), and (**11**) the double alkylation was effected in one step using two equivalents of base with excess electrophile. Given that lower yields were observed for the second alkylation step in the case of the unsymmetrical dienes (**6**), (**8**), and (**10**), the initial first alkylation was always carried out with the less reactive halide and the more reactive allyl halides were used in the second alkylation step.

With the dienes (**6**-**11**) in hand, ring closing metathesis[29–34] proceeded smoothly in excellent yield using 5% Grubbs catalyst $[Cl_2(PCy_3)_2RuCHPh]$ at room temperature affording spirolactams (**12**-**17**) with various appended ring sizes.

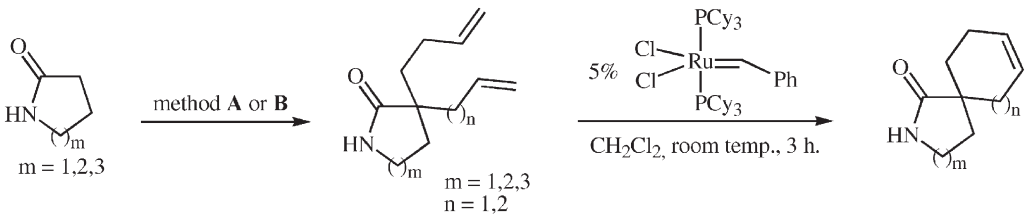
Our efforts next focused on the subsequent conversion of the spirolactams to spiroimines (Table 2).[35–37] After much experimentation, it was found that the optimum procedure involved protection of the five and six membered lactams (**12**-**15**) as the fluoride-labile β-trimethylsilylethoxycarbonyl (TEOC) group[38] followed by reduction of the amide carbonyl group using lithium triethylborohydride[39] as described by Grieco and Kaufman.[40] The TEOC group was introduced employing butyllithium and 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate providing the TEOC protected lactams (**18**-**21**). Subsequent reduction with lithium triethylborohydride at −78 °C followed by immediate exposure to tetrabutylammonium fluoride afforded the spirocyclic imines (**22**-**25**) in good yield. Spiroimines (**22**-**25**) were readily purified by flash chromatography and did not undergo decomposition upon prolonged storage at room temperature.

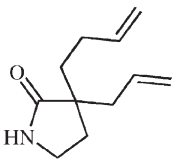
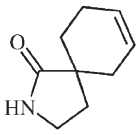
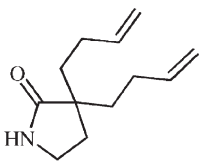
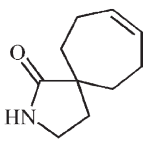
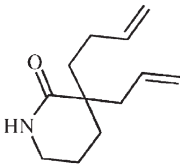
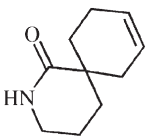
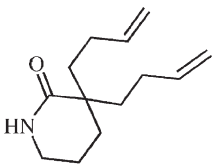
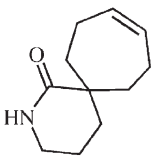
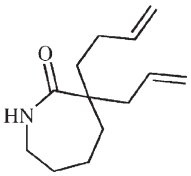
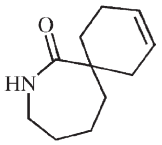
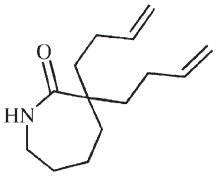
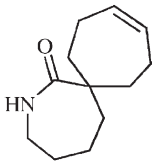
This reduction procedure proved a reliable method for the preparation of spirolactams containing a five or six membered lactam ring, however, in the case of TEOC protected spirolactam (**26**) in which the lactam was



Scheme 1.

Table 1. Preparation of spirolactams



Entry	Dialkylated lactam (yield %, method[a,b])	Spirolactam (yield %)
1	 **6** 74%, A	 **12**, 86%
2	 **7** 71%, B	 **13**, 93%
3	 **8** 81%, A	 **14**, 90%
4	 **9** 78%, B	 **15**, 95%
5	 **10** 67%, A	 **16**, 88%
6	 **11** 77%, B	 **17**, 92%

[a] Method A: (i) *n*-BuLi (1.05 equiv.), THF, −78 °C, $SiMe_3Cl$ (1.05 equiv.) −78 °C to 0 °C; (ii) LDA (1 equiv.), THF, −78 °C, 4-bromo-1-butene (1.05 equiv.) −78 °C to 0 °C; (iii) LDA (1.1 equiv.) −78 °C, allyl iodide (1.25 equiv.), −78 °C to 0 °C.

[b] Method B: (i) *n*-BuLi (1.05 equiv.), −78 °C, $SiMe_3Cl$ (1.05 equiv.), −78 °C to 0 °C; (ii) LDA (2.3 equiv.) −78 °C, 4-bromo-1-butene (2.5 equiv.), −78 °C to 0 °C.

embedded in a seven membered ring an alternative mode of reduction took place. In this case reduction of the carbamate carbonyl group took place in preference to the lactam carbonyl group resulting in formation of *N*-formyl spirolactam (**27**) (Scheme 2). This result is readily rationalized by examination of the minimum energy conformation of the 6,6-spirolactam (**20**) compared to the 7,6-spirolactam (**26**) (Fig. 1). Simple molecular models and semi-empirical calculations (computed for R=Me on the PM3 level)

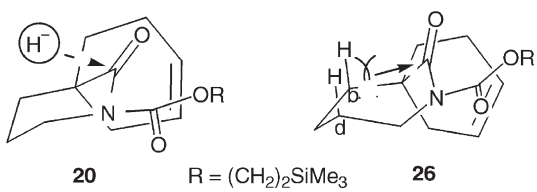
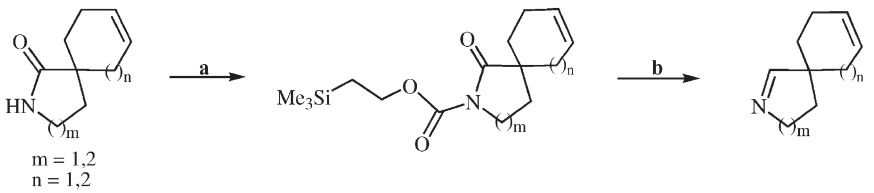
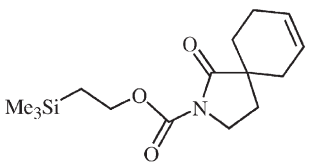
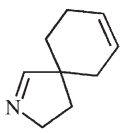
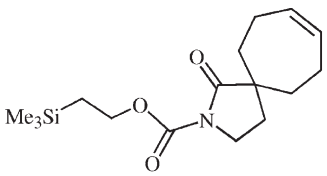
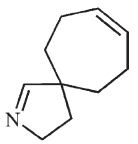
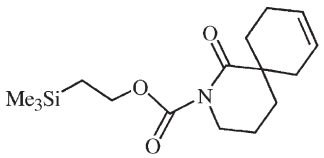
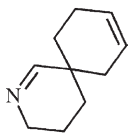
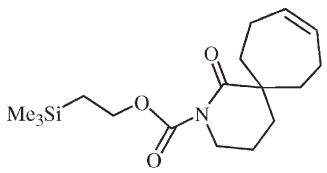
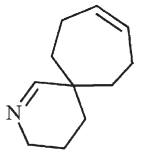


Figure 1. Proposed structures for attack of hydride on the lactam carbonyl group of **20** and **26**.

Table 2. Preparation of spiroimines[a,b]

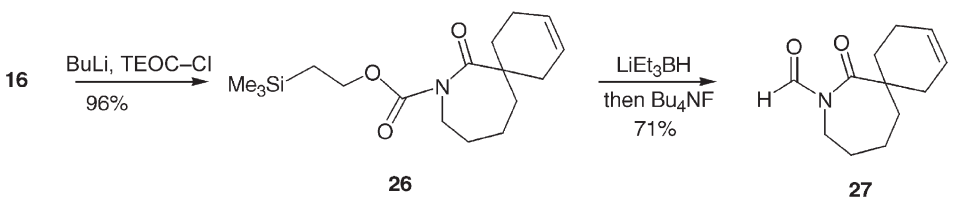


Entry	TEOC lactam (yield %)		Spiroimine (yield %)	
1		**18**, 98%		**22**, 83%
2		**19**, 99%		**23**, 70%
3		**20**, 97%		**24**, 86%
4		**21**, 98%		**25**, 84%

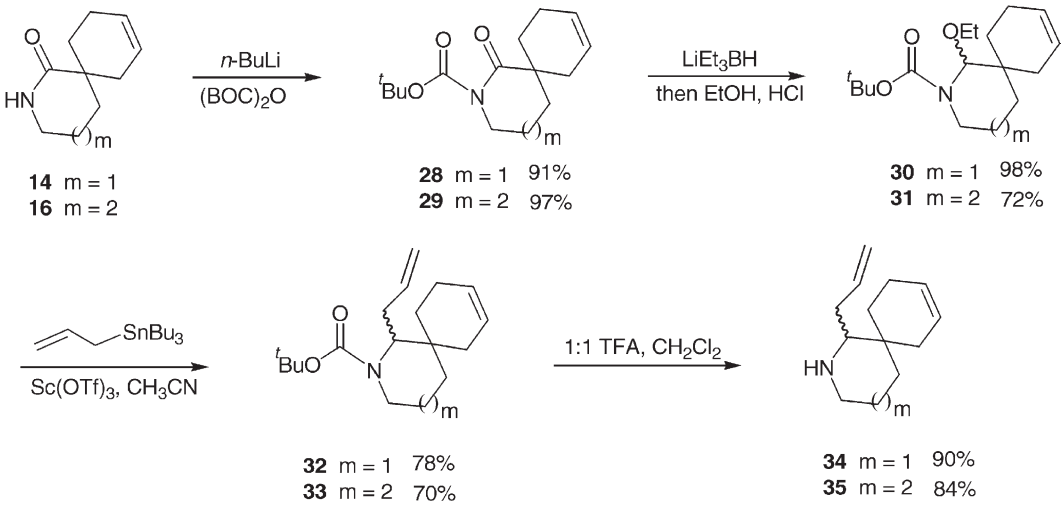
[a] (i) *n*-BuLi (1.05 equiv.), THF, −78 °C; (ii) 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (1.15 equiv.), −78 °C to rt.
[b] (i) $LiEt_3H$ (1.2 equiv.), −78 °C then work-up; (ii) Bu_4NF (2 equiv.), THF, rt, 12 h.

suggest that in the seven membered spirolactam (**26**) the carbonyl group experiences considerable steric hindrance due to transannular interactions with the hydrogens on the carbons α and δ to the lactam carbonyl group thus forcing the hydride to attack the more accessible carbonyl group of the carbamate protecting group. However, the six membered ring in spirolactam (**20**) adopts a chair conformation in which the carbonyl group is readily accessible to the incoming hydride source resulting in smooth conversion to the desired spirocyclic imine (**26**) after treatment with tetrabutylammonium fluoride.

The inherent inability to direct hydride addition to the lactam carbonyl group in spirolactam (**26**) rather than the carbonyl group in the TEOC group did not bode well for the future addition of organometallic agents to this carbonyl group as a means to introduce functionality to this carbon in the spirolides (**2**-**5**). This observation prompted protection of the lactam nitrogen with a bulky *tert*-butoxycarbonyl group (BOC) hoping to effect reduction of the lactam rather than the carbamate group (Scheme 3) as reported by Overman et al.[41] on a similar molecule. Successful reduction of the lactam to a hemiaminal then allowed an opportunity for generation and trapping of an acyliminium ion to introduce further functionality at this position as required for the synthesis of the spirolides (**2**-**5**). This methodology could equally be applied to the 6,6-spirolactam ring system (**14**) of gymnodimine (**1**). Our efforts therefore focused on the generation of hemiaminals from spirolactams (**14**) and (**16**) and 'in situ' addition of allylstannane as method to introduce functionality at this position (Scheme 3). Precedent for the regeneration of the spiroimine from the substituted spirolactams was demonstrated from related work by Pradhan et al.[21]



Scheme 2.



Scheme 3.

Protection of spirolactams (**14**) and (**16**) as BOC derivatives (**28**) and (**29**) proceeded uneventfully using *n*-BuLi and *tert*-butyloxycarbonyl anhydride. Subsequent treatment with lithium superhydride effected reduction of the lactam carbonyl group to give hemiaminals (**30**) and (**31**) in 70% yield upon treatment with ethanolic HCl.[41] Reaction of the hemiaminals (**30**) and (**31**) with excess allyltributylstannane in the presence of scandium(III)triflate in acetonitrile at 0 °C effected generation of the acyliminium ion[42] and subsequent conversion to the allylated adducts (**32**) and (**33**). The ^{1}H and ^{13}C NMR spectra of the hemiaminals (**30**), (**31**) and the allylated products (**32**), (**33**) were complicated by the presence of conformers of the two diastereomers due to the restricted rotation imposed by the bulky BOC group. Subsequent removal of the BOC group provided amines (**34**) and (**35**) for which the NMR spectra then only showed the presence of the two diastereomers as a 1:1 mixture.

The successful conversion of spirolactams (**14**) and (**16**) to the allylated adducts (**32**) and (**33**) provides an approach for appendage of functionality to the lactam carbonyl group as required for the synthesis of gymnodimine (**1**) and the spirolides (**2**–**5**). The use of an acyliminium ion intermediate to effect this transformation thus provides an attractive alternative to the addition of an organometallic species to the lactam carbonyl group that would be hampered by the steric bulk imposed by the neighbouring quaternary spiro centre.

In conclusion we have demonstrated that α,α-dialkylated lactams can be utilized in conjunction with ring closing metathesis as an efficient method for the construction of spiroimines. The procedure combines the use of a convenient lactam double alkylation protocol with a highly efficient ring-closing metathesis step. Additionally, a useful method for the reduction of the sterically hindered spirolactams to spirocyclic imines has been extended from the work of Grieco and Kaufmann.[40] This methodology provides access to 6,6-spiroimine (**26**) that is the key pharmacophore in the shellfish toxin gymnodimine (**1**). As part of model studies directed towards the synthesis of the macrolide shellfish toxins, the spirolides (**1**-**5**), 7,6-spirolactam (**16**) underwent scandium triflate promoted allylation of a derived acyliminium ion. Incorporation of this methodology into the synthesis of the spirolides is currently under investigation in our laboratory.

3. Experimental

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum One Fourier-transform infrared spectrophotometer as thin films or Nujol mulls between sodium chloride plates. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (300 MHz) or a Bruker DRX-400 (400 MHz) spectrometer at ambient temperature. Carbon (^{13}C) NMR spectra were recorded on a Bruker Avance 300 (75 MHz) or a Bruker DRX 400 (100 MHz) spectrometer at ambient temperature with complete proton decoupling. All spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^{1}H at 7.26 ppm and ^{13}C at 77.0 ppm). Low resolution mass spectra were recorded on a VG70-SE double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV. High resolution mass spectra were recorded at nominal resolution of 5000 or 10,000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de-Haen Kieselgel S silica gel (both 230–400 mesh) with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine, alkaline permanganate or vanillin in methanolic sulfuric acid. Tetrahydrofuran was distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride immediately before use.

3.1. General procedure for the dialkylation of lactams

To a stirred solution of the lactam (5 mmol) in dry THF (30 mL) was added dropwise *n*-BuLi (1.6 M solution in

hexane, 3.28 mL, 5.25 mmol) at −78 °C. After stirring for 15 min at −78 °C, trimethylsilyl chloride (0.67 mL, 5.25 mmol) was added dropwise and stirring continued for 30 min while the solution was allowed to warm to 0 °C.

Method A. The reaction mixture was then cooled to −78 °C and transferred (via cannula) to a solution of freshly prepared LDA (5 mmol) in dry THF (20 mL) at −78 °C. After stirring for 30 min at −78 °C, 4-bromo-1-butene (0.53 mL, 5.25 mmol) was added dropwise and stirring continued for 1 h while the solution was allowed to warm to 0 °C. The reaction mixture was then cooled to −78 °C and transferred to a solution of freshly prepared LDA (5.5 mmol) in dry THF (20 mL) at −78 °C. After stirring for 45 min at −78 °C, allyl iodide (0.57 mL, 6.25 mmol) was added dropwise and stirring continued for 3 h while the solution was allowed to warm to 23 °C.

Method B. The reaction mixture was then cooled to −78 °C and transferred (via cannula) to a solution of freshly prepared LDA (11.5 mmol) in dry THF (30 mL) at −78 °C. After stirring for 30 min at −78 °C, 4-bromo-1-butene (1.26 mL, 12.5 mmol) was added dropwise and stirring continued for 4 h while the solution was allowed to warm to 23 °C.

The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the dialkylated lactam was obtained after purification of the residue by column chromatography using ether or hexane/ether 1:1 as eluant.

3.1.1. 3-Allyl-bis(3-butenyl)-2-pyrrolidinone (6). 74% Yield; colorless oil; IR ν_{max}/cm^{-1} 3231, 3076, 2914, 1693, 1450, 1282, 996, 912; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (bs, 1H), 5.87–5.72 (m, 2H), 5.15–4.92 (m, 4H), 3.29–3.24 (m, 2H), 2.38–1.94 (m, 6H), 1.70–1.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 138.2, 133.9, 118.4, 114.6, 46.3, 41.2, 39.1, 35.9, 30.0, 28.6; MS (EI) *m/z* 179 (5%, $[M]^+$), 125 (100); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310; found, 179.1305.

3.1.2. 3,3-Bis(3-butenyl)-2-pyrrolidinone (7). 71% Yield; colorless oil; IR ν_{max}/cm^{-1} 3223, 3077, 2935, 1692, 1453, 1283, 994, 909; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (bs, 1H), 5.86–5.72 (m, 2H), 5.05–4.90 (m, 4H), 3.28 (t, 2H, *J*=7.1 Hz), 2.18–1.96 (m, 6H), 1.65–1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 138.3, 114.5, 46.2, 39.1, 35.7, 30.8, 28.5; MS (EI) *m/z* 193 (1%, $[M]^+$), 139 (32), 98 (100); HRMS Calcd for $C_{12}H_{19}NO$ 193.1467; found, 193.1465.

3.1.3. 3-Allyl-3-(3-butenyl)tetrahydro-2(1*H*)-pyridinone (8). 81% Yield; colorless oil; IR ν_{max}/cm^{-1} 3278, 3074, 2942, 1659, 1489, 1448, 997, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (bs, 1H), 5.84–5.73 (m, 2H), 5.09–4.91 (m, 4H), 3.28–3.23 (m, 2H), 2.53–2.47 (m, 1H), 2.25–2.19 (m, 1H), 2.15–1.99 (m, 2H), 1.84–1.67 (m, 5H), 1.57–1.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 138.6, 134.3, 118.1, 114.4, 44.4, 43.0, 42.7, 37.6, 29.3, 28.7, 19.7; MS (EI) *m/z* 193 (4%, $[M]^+$), 139 (100); HRMS Calcd for $C_{12}H_{19}NO$ 193.1467; found, 193.1468.

3.1.4. 3,3-Bis(3-butenyl)tetrahydro-2(1*H*)-pyridinone (9). 78% Yield; colorless oil; IR ν_{max}/cm^{-1} 2946, 2869, 1654, 1488, 1265, 915, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (bs, 1H), 5.84–5.74 (m, 2H), 5.03–4.90 (m, 4H), 3.28–3.24 (m, 2H), 2.14–1.98 (m, 4H), 1.82–1.71 (m, 6H), 1.59–1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 138.6, 114.4, 44.2, 42.6, 37.7, 29.7, 28.6, 19.8; MS (EI) *m/z* 207 (1%, $[M]^+$), 153 (20), 112 (100); HRMS Calcd for $C_{13}H_{21}NO$ 207.1623; found, 207.1624.

3.1.5. 3-Allyl-3-(3-butenyl)-2-azepanone (10). 67% Yield; colorless oil; IR ν_{max}/cm^{-1} 3281, 3073, 2868, 1650, 1478, 1435, 1411, 1362, 1281, 995, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (bs, 1H), 5.86–5.76 (m, 2H), 5.09–4.91 (m, 4H), 3.31–3.23 (m, 1H), 3.21–3.13 (m, 1H), 2.48–2.43 (m, 1H), 2.36–2.31 (m, 1H), 2.17–2.07 (m, 1H), 2.04–1.95 (m, 1H), 1.80–1.54 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 138.7, 134.9, 117.7, 114.3, 47.8, 42.2, 41.3, 34.3, 32.6, 29.1, 28.3, 23.7; MS (EI) *m/z* 207 (5%, $[M]^+$), 153 (100); HRMS Calcd for $C_{13}H_{21}NO$ 207.1623; found, 207.1618.

3.1.6. 3,3-Bis(3-butenyl)-2-azepanone (11). 77% Yield; colorless oil; IR ν_{max}/cm^{-1} 2931, 2869, 1651, 1478, 1460, 1408, 1282, 995, 908; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (bs, 1H), 5.90–5.77 (m, 2H), 5.06–4.92 (m, 4H), 3.25–3.19 (m, 2H), 2.17–1.59 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 138.9, 114.3, 47.7, 42.3, 35.5, 32.5, 29.1, 28.5, 23.7; MS (EI) *m/z* 221 (1%, $[M]^+$), 167 (22), 126 (100); HRMS Calcd for $C_{14}H_{23}NO$ 221.1780; found, 221.1776.

3.2. General procedure for the metathesis reaction

To a stirred solution of dialkylated lactam (3 mmol) in dry dichloromethane (30 mL) was added benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (0.12 g, 0.15 mmol) at 23 °C and the reaction mixture stirred for 3 h. DMSO (0.5 mL) was added and stirring continued for 12 h. The solvents were removed under reduced pressure and the bicyclic lactam was obtained after purification of the residue by column chromatography using ether or hexane/ether 1:1 as eluant.

3.2.1. 2-Azaspiro[4.5]dec-7-en-1-one (12). 86% Yield; colorless oil; IR ν_{max}/cm^{-1} 2930, 2898, 1680, 1431, 1293, 810; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (bs, 1H), 5.75–5.63 (m, 2H), 3.34 (t, 2H, *J*=6.8 Hz), 2.41–2.31 (m, 1H), 2.24–1.80 (m, 6H), 1.57–1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 126.3, 124.6, 41.9, 38.9, 32.1, 31.9, 28.1, 22.0; MS (EI) *m/z* 151 (100%, $[M]^+$), 122 (28), 93 (25), 79 (35); HRMS Calcd for $C_9H_{13}NO$ 151.0997; found, 151.0996.

3.2.2. 2-Azaspiro[4.6]undec-8-en-1-one (13). 93% Yield; colorless oil; IR ν_{max}/cm^{-1} 3015, 2932, 2845, 1652, 1444, 1292, 1284, 1073, 711; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (bs, 1H), 5.78–5.68 (m, 2H), 3.30 (t, 2H, *J*=6.8 Hz), 2.42–2.31 (m, 2H), 2.19–1.87 (m, 6H), 1.63–1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3, 131.4, 46.5, 38.6, 33.9, 33.4, 24.4; MS (EI) *m/z* 165 (15%, $[M]^+$), 98 (100); HRMS Calcd for $C_{10}H_{15}NO$ 165.1154; found, 165.1155.

3.2.3. 2-Azaspiro[5.5]undec-8-en-1-one (14). 90% Yield; colorless oil; IR ν_{max}/cm^{-1} 2948, 1650, 1489, 1265, 729,

704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (bs, 1H), 5.68–5.58 (m, 2H), 3.29–3.26 (m, 2H), 2.60–2.56 (m, 1H), 2.14–1.54 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 125.3, 124.6, 42.6, 39.7, 33.3, 30.1, 28.9, 21.3, 19.0; MS (EI) *m/z* 165 (100%, $[M]^+$), 136 (80); HRMS Calcd for $C_{10}H_{15}NO$ 165.1154; found, 165.1155.

3.2.4. 2-Azaspiro[5.6]dodec-9-en-1-one (15). 95% Yield; colorless oil; IR ν_{max}/cm^{-1} 3017, 2941, 2870, 1649, 1488, 1314, 922, 745, 722; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (bs, 1H), 5.67–5.60 (m, 2H), 3.31–3.26 (m, 2H), 2.41–2.33 (m, 2H), 2.23–2.07 (m, 4H), 1.82–1.73 (m, 4H), 1.66–1.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 130.7, 43.5, 42.5, 36.0, 31.7, 24.4, 18.7; MS (EI) *m/z* 179 (7%, $[M]^+$), 112 (100); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310; found, 179.1310.

3.2.5. 8-Azaspiro[5.6]dodec-2-en-7-one (16). 88% Yield; colorless oil; IR ν_{max}/cm^{-1} 2932, 1642, 1478, 1271, 723, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (bs, 1H), 5.67–5.63 (m, 2H), 3.36–3.16 (m, 2H), 2.76–2.64 (m, 1H), 2.16–1.51 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 125.3, 125.2, 43.4, 42.7, 33.7, 31.8, 29.6, 27.4, 24.4, 22.3; MS (EI) *m/z* 179 (100%, $[M]^+$), 150 (50); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310; found, 179.1308.

3.2.6. 2-Azaspiro[6.6]tridec-10-en-1-one (17). 92% Yield; colorless oil; IR ν_{max}/cm^{-1} 3053, 2930, 2844, 1641, 1434, 1265, 737, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (bs, 1H), 5.68–5.59 (m, 2H), 3.27–3.21 (m, 2H), 2.41–2.06 (m, 6H), 1.81–1.57 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 130.9, 48.0, 42.8, 34.5, 33.8, 29.5, 24.2, 24.15; MS (EI) *m/z* 193 (6%, $[M]^+$), 126 (100); HRMS Calcd for $C_{12}H_{19}NO$ 193.1467; found, 193.1465.

3.3. General procedure for the TEOC-protection of spirolactams

To a stirred solution of the bicyclic lactam (3 mmol) in dry THF (30 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.97 mL, 3.15 mmol) at −78 °C. After stirring for 30 min at −78 °C a solution of 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate (0.98 g, 3.45 mmol) in dry THF (5 mL) was added dropwise and stirring continued for 1.5 h while the solution was allowed to warm up to 23 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the TEOC protected lactam was obtained after purification of the residue by column chromatography using hexane/ether 10:3 as eluant.

3.3.1. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[4.5]dec-7-ene-2-carboxylate (18). 98% Yield; colorless oil; IR ν_{max}/cm^{-1} 2953, 2933, 2899, 1752, 1699, 1304, 1249, 1063, 838, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73–5.61 (m, 2H), 4.35–4.30 (m, 2H), 3.77–3.65 (m, 2H), 2.41–2.33 (m, 1H), 2.22–1.98 (m, 2H), 1.92–1.85 (m, 4H), 1.58–1.51 (m, 1H), 1.13–1.08 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 152.1, 126.2, 123.9, 65.1, 44.5, 42.9, 32.0, 28.5, 28.1, 21.7, 17.5, −1.9; MS (EI) *m/z* 295 (1%, $[M]^+$), 267 (42), 73 (100); HRMS Calcd for $C_{15}H_{25}NO_3Si$ 295.1604; found, 295.1607.

3.3.2. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[4.6]undec-8-ene-2-carboxylate (19). 99% Yield; colorless oil; IR ν_{max}/cm^{-1} 2961, 2923, 1748, 1710, 1303, 1250, 1063, 939, 836, 766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.67 (m, 2H), 4.34–4.30 (m, 2H), 3.68 (t, 2H, J=7.0 Hz), 2.42–2.32 (m, 2H), 2.14–2.04 (m, 2H), 1.99–1.91 (m, 4H), 1.64–1.58 (m, 2H), 1.13–1.08 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 152.2, 131.1, 65.1, 49.0, 42.7, 33.9, 30.3, 24.8, 17.6, −1.6; MS (EI) *m/z* 310 (1%), 281 (2), 214 (100), 154 (42); HRMS Calcd for $C_{16}H_{27}NO_3Si$ 309.1760; could not be detected.

3.3.3. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[5.5]undec-8-ene-2-carboxylate (20). 97% Yield; colorless oil; IR ν_{max}/cm^{-1} 3025, 2952, 2899, 1769, 1713, 1379, 1295, 1268, 1162, 1049, 944, 860, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69–5.58 (m, 2H), 4.33–4.29 (m, 2H), 3.76–3.60 (m, 2H), 2.65–2.56 (m, 1H), 2.10–1.62 (m, 9H), 1.12–1.07 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 155.3, 125.4, 124.4, 65.4, 47.4, 43.3, 33.6, 30.7, 29.7, 21.6, 19.4, 17.5, −1.6; MS (EI) *m/z* 309 (1%, $[M]^+$), 281 (30), 73 (100); HRMS Calcd for $C_{16}H_{27}NO_3Si$ 309.1760; found, 309.1763.

3.3.4. 2-(Trimethylsilyl)ethyl 1-oxo-2-azaspiro[5.6]dodec-9-ene-2-carboxylate (21). 98% Yield; colorless oil; IR ν_{max}/cm^{-1} 3015, 2952, 1768, 1714, 1379, 1274, 1160, 935, 860, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67–5.60 (m, 2H), 4.33–4.28 (m, 2H), 3.67 (t, 2H, J=5.9 Hz), 2.40–2.04 (m, 6H), 1.85–1.76 (m, 4H), 1.68–1.60 (m, 2H) 1.11–1.07 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 155.4, 130.6, 65.3, 47.5, 47.3, 35.9, 32.6, 24.2, 19.2, 17.5, −1.6; MS (EI) *m/z* 323 (1%), 228 (90), 73 (100); HRMS Calcd for $C_{17}H_{29}NO_3Si$ 323.1917; found, 323,1911.

3.4. General procedure for the reduction of TEOC protected lactams

To a stirred solution of the TEOC protected lactam (1 mmol) in dry THF (10 mL) was added dropwise a 1 M solution of $LiEt_3BH$ in THF (1.2 mL, 1.2 mmol) at −78 °C. After stirring for 45 min at −78 °C the reaction mixture was quenched by dropwise addition of water followed by aqueous work up and extraction of the aqueous phase with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. The crude residue was dissolved in THF (10 mL) and treated with a 1 M solution of tetrabutylammonium fluoride in THF (2 mL, 2 mmol). After stirring for 12 h at 23 °C toluene (10 mL) was added and all solvents removed under reduced pressure. The spiroimine was obtained after purification of the residue by column chromatography using ether as eluant.

3.4.1. 2-Azaspiro[4.5]deca-1,7-diene (22). 83% Yield; colorless oil; IR ν_{max}/cm^{-1} 3019, 2918, 2839, 1650, 1435, 1351, 1257, 1206, 921; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (bs, 1H), 5.74–5.61 (m, 2H), 3.86 (t, 2H, J=7.1 Hz), 2.14–2.04 (m, 3H), 1.95–1.86 (m, 1H), 175–1.63 (m, 3H), 1.53–1.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 126.8, 124.8, 59.8, 34.4, 33.1, 30.2, 29.8, 22.7; MS (EI) *m/z* 135 (85%, $[M]^+$), 80 (100); HRMS Calcd for $C_9H_{13}N$ 135.1048; found, 135.1047.

3.4.2. 2-Azaspiro[4.6]undeca-1,8-diene (23). 70% Yield; colorless oil; IR ν_{max}/cm^{-1} 3017, 2919, 2847, 1690, 1443, 1284, 1267, 1053, 921, 899, 729; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (bs, 1H), 5.74 (t, 2H, J=3.1 Hz), 3.83 (dt, 2H, J_d=2.0 Hz, J_t=7.1 Hz), 2.22–2.15 (m, 4H), 1.73–1.64 (m, 4H), 1.58–1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 131.5, 59.6, 34.4, 33.8, 24.9, 24.2; MS (EI) m/z 149 (75%, $[M]^+$), 93 (100), 79 (90); HRMS Calcd for $C_{10}H_{15}N$ 149.1204; found, 149.1201.

3.4.3. 2-Azaspiro[5.5]undeca-1,8-diene (24). 86% Yield; colorless oil; IR ν_{max}/cm^{-1} 3023, 2923, 2852, 1649, 1438, 1220, 1047, 923; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (bs, 1H), 5.73–5.57 (m, 2H), 3.61–3.43 (m, 2H), 2.10–1.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 126.3, 124.0, 49.9, 34.7, 33.4, 31.1, 29.5, 21.2, 19.0; MS (EI) m/z 149 (96%, $[M]^+$), 120 (100); HRMS Calcd for $C_{10}H_{15}N$ 149.1204; found, 149.1204.

3.4.4. 2-Azaspiro[5.6]dodeca-1,9-diene (25). 84% Yield; colorless oil; IR ν_{max}/cm^{-1} 3014, 2919, 2851, 1650, 1453, 1343, 1259, 1052, 973, 924, 899, 717; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (bs, 1H), 5.68 (t, 2H, J=3.0 Hz), 3.57–3.42 (m, 2H), 2.25–2.10 (m, 4H), 1.72–1.54 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 131.0, 49.8, 36.0, 35.3, 30.0, 23.4, 18.9; MS (EI) m/z 163 (81%, $[M]^+$), 134 (100), 96 (72); HRMS Calcd for $C_{11}H_{17}N$ 163.1361; found, 163.1356.

3.5. General procedure for the Boc-protection of spirolactams

To a stirred solution of the bicyclic lactam (3 mmol) in dry THF (30 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.97 mL, 3.15 mmol) at −78 °C. After stirring for 30 min at −78 °C a solution of *tert*-butyloxycarbonyl anhydride (0.79 g, 3.60 mmol) in dry THF (5 mL) was added dropwise and stirring continued for 1.5 h while the solution was allowed to warm up to 23 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$. The solvents were removed under reduced pressure and the Boc protected lactam was obtained after purification of the residue by column chromatography using hexane/ether 10:2 as eluant.

3.5.1. *tert*-Butyl 1-oxo-2-azaspiro[5.5]undec-8-ene-2-carboxylate (28). 91% Yield; colorless oil; IR ν_{max}/cm^{-1} 2977, 2936, 1766, 1714, 1367, 1296, 1277, 1149; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69–5.57 (m, 2H), 3.69–3.54 (m, 2H), 2.64–2.55 (m, 1H), 2.07–1.61 (m, 9H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 153.7, 125.4, 124.6, 82.4, 47.3, 43.2, 33.6, 30.7, 29.9, 28.0, 21.6, 19.4; MS (EI) m/z 265 (1%, $[M]^+$), 209 (87), 57 (100); HRMS Calcd for $C_{15}H_{23}NO_3$ 265.1678; found, 265.1678.

3.5.2. *tert*-Butyl 7-oxo-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (29). 97% Yield; colorless oil; IR ν_{max}/cm^{-1} 2976, 2931, 1753, 1713, 1367, 1317, 1296, 1277, 1257, 1151; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68–5.59 (m, 2H), 3.66–3.54 (m, 2H), 2.63–2.54 (m, 1H), 2.13–1.90 (m, 3H), 1.74–1.48 (m, 8H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.4, 154.0, 126.0, 125.6, 81.4, 47.5, 44.4, 33.7, 32.8, 29.9, 28.0, 26.3, 23.2, 22.3; MS (EI) m/z 279 (1%, $[M]^+$), 223 (54), 57 (100); HRMS Calcd for $C_{16}H_{25}NO_3$ 279.1834; found, 279.1831.

3.6. General procedure for the reduction of BOC-protected lactams

To a stirred solution of the Boc protected lactam (1 mmol) in dry THF (10 mL) was added dropwise a 1 M solution of $LiEt_3BH$ in THF (3 mL, 3 mmol) at −78 °C. After stirring for 30 min at −78 °C the reaction mixture was quenched by the addition of a solution of conc. HCl (1 mL) in ethanol (10 mL) and warmed up to 23 °C. After addition of ether (50 mL) followed by aqueous work up and extraction of the aqueous phase with Et_2O, the combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. The hemiaminal was obtained after purification of the residue by column chromatography using hexane/ether 10:2 as eluant.

3.6.1. *tert*-Butyl 1-ethoxy-2-azaspiro[5.5]undec-8-ene-2-carboxylate (30). 98% Yield; colorless oil (mixture of diastereomers and rotamers);[†] IR ν_{max}/cm^{-1} 2973, 2930, 1700, 1654, 1451, 1414, 1364, 1281, 1250, 1156, 1078; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72–5.53 (m, 2H), 5.16, 5.08, 5.06 and 4.93 (each s, 1H), 3.97–3.89 and 3.81–3.74 (2m, 1H), 3.52–3.25 (m, 2H), 2.99–2.81 (m, 1H), 2.12–1.92 (m, 3H), 1.83–1.36 (m, 16H), 1.16 and 1.15 (2q, 3H, J=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 155.2, 126.7, 126.6, 125.9, 125.7, 125.2, 125.0, 124.9, 124.8, 86.1, 85.7, 84.1, 83.8, 79.5, 79.4, 79.3, 62.6, 62.1, 62.0, 38.8, 38.6, 37.4, 37.3, 35.4, 35.3, 35.2, 35.1, 32.0, 31.9, 31.1, 31.0, 30.5, 28.4, 27.9, 27.4, 27.0, 26.9, 21.8, 21.7, 20.8, 20.7, 20.5, 20.4, 15.1, 15.0, 14.8; MS (EI) m/z 295 (1%, $[M]^+$), 193 (100), 57 (80); HRMS Calcd for $C_{17}H_{29}NO_3$ 295.2147; found, 295.2147.

3.6.2. *tert*-Butyl 7-ethoxy-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (31). 72% Yield; colorless oil (mixture of diastereomers and rotamers);[†] IR ν_{max}/cm^{-1} 2973, 2928, 1696, 1451, 1414, 1365, 1330, 1211, 1166, 1130, 1081; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73–5.49 (m, 2H), 5.22, 5.15, 5.08 and 4.94 (each s, 1H), 3.53–3.15 (m, 4H), 2.09–1.36 (m, 21H), 1.17–1.13 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 155.8, 126.6, 126.5, 126.0, 125.5, 125.4, 125.1, 90.4, 89.8, 86.9, 86.5, 79.5, 79.4, 79.1, 79.0, 63.0, 62.8, 62.6, 62.4, 40.4, 40.3, 40.2, 39.9, 39.7, 39.2, 36.2, 35.9, 32.9, 32.5, 32.2, 31.9, 31.7, 31.5, 28.5, 28.4, 28.1, 27.4, 27.2, 25.7, 25.4, 25.2, 22.6, 21.9, 21.8, 20.5, 20.3, 19.9, 19.7, 14.9, 14.8, 14.7; MS (EI) m/z 309 (1%, $[M]^+$), 207 (75), 57 (100); HRMS Calcd for $C_{18}H_{31}NO_3$ 309.2304; found, 309.2302.

3.7. General procedure for the allylation reaction

To a stirred solution of the hemiaminal (0.4 mmol) in dry acetonitrile (5 mL) was added allyltributylstannane (0.37 mL, 1.2 mmol) and scandium(III)triflate (20 mg, 0.04 mmol) at 0 °C. The reaction was monitored by TLC (hexane/ether 10:2) and stirred at 0 °C until completion

[†] The presence of both diastereomers and rotamers afforded complex ^1H and ^{13}C NMR spectra with overlapping signals that are only reported once.

(8–12 h). In some cases further addition of scandium(III)-triflate (20 mg, 0.04 mmol) after 6 h was necessary to obtain complete reaction. The reaction mixture was evaporated under reduced pressure and the Boc-protected allylated amine was obtained after purification of the residue by column chromatography using hexane/ether 10:2 as eluant.

3.7.1. *tert*-Butyl 1-allyl-2-azaspiro[5.5]undec-8-ene-2-carboxylate (32). 78% Yield; colorless oil (mixture of diastereomers and rotamers);† IR ν_{max}/cm^{-1} 2974, 2930, 2863, 1693, 1417, 1364, 1248, 1176, 1159, 1147, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77–5.50 (m, 3H), 5.06–4.93 (m, 2H), 4.12–4.03 (m, 1H), 3.94–3.84 (m, 1H), 2.77–2.62 (m, 1H), 2.51–2.35 (m, 1H), 2.29–1.20 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.6, 135.9, 135.8, 135.5, 135.4, 126.6, 126.5, 125.9, 125.7, 125.4, 124.3, 124.2, 116.4, 116.3, 115.9, 79.0, 78.9, 78.7, 58.2, 56.9, 54.8, 53.9, 38.9, 38.6, 37.5, 37.1, 36.4, 36.3, 34.1, 34.0, 33.8, 33.6, 33.5, 31.9, 31.3, 30.7, 30.4, 30.3, 30.2, 29.7, 28.6, 28.5, 28.4, 27.3, 26.9, 22.2, 22.1, 21.0, 20.9, 20.6, 20.5; MS (EI) *m/z* 291 (1%, [M]$^+$), 194 (100), 150 (34); HRMS (CI) Calcd for $C_{18}H_{30}NO_2$ (M+H) 292.2276; found, 292.2275 ([M+H]$^+$).

3.7.2. *tert*-Butyl 7-allyl-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (33). 70% Yield; colorless oil (mixture of diastereomers and rotamers);† IR ν_{max}/cm^{-1} 2973, 2927, 2865, 1688, 1414, 1364, 1166, 1135, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.48 (m, 3H), 5.06–4.92 (m, 2H), 4.33–4.20 and 4.03–3.90 (each m, 1H), 3.79–3.46 (m, 1H), 2.97–2.76 (m, 1H), 2.38–1.17 (m, 23H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 156.4, 156.2, 136.8, 136.4, 136.3, 136.0, 135.8, 135.6, 135.5, 126.8, 126.7, 125.9, 125.8, 125.7, 124.8, 124.7, 116.6, 116.4, 116.3, 116.2, 116.0, 115.9, 79.1, 79.0, 78.6, 63.0, 61.4, 58.5, 58.0, 41.6, 41.2, 41.0, 40.9, 39.3, 39.1, 38.4, 37.4, 36.9, 36.5, 35.1, 34.2, 34.1, 32.8, 32.2, 32.0, 31.4, 31.3, 31.1, 30.8, 30.7, 30.4, 30.3, 29.7, 29.5, 29.2, 29.0, 28.6, 28.5, 28.3, 27.5, 26.7, 26.1, 26.0, 22.5, 22.4, 22.3, 20.7, 20.3, 20.1, 19.9; MS (EI) *m/z* 305 (1%, [M]$^+$), 208 (100), 57 (95); HRMS Calcd for $C_{19}H_{31}NO_2$ 305.2355; found, 305.2357.

3.8. General procedure for the Boc-deprotection

To a stirred solution of the Boc-protected amine (0.3 mmol) in DCM (3 mL) was added TFA (3 mL). After stirring for 30 min at 23 °C toluene (20 mL) was added and the reaction mixture evaporated under reduced pressure. The spiroamine was obtained after purification of the residue by column chromatography using hexane/DCM/MeOH/Et_3N 10:20:4:0.2 as eluant.

3.8.1. 1-Allyl-2-azaspiro[5.5]undec-8-ene (34). 90% Yield; colorless oil (mixture of diastereomers);† IR ν_{max}/cm^{-1} 3019, 2927, 2844, 1451, 1435, 1313, 1132, 913, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78–5.68 (m, 1H), 5.64–5.55 (m, 2H), 5.12–5.04 (m, 2H), 3.04–2.98 (m, 1H), 2.62–2.54 (m, 1H), 2.41–2.24 (m, 2H), 2.13–1.12 (m, 11H), 1.01–0.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 137.1, 126.1, 125.9, 125.8, 125.3, 117.5, 117.3, 64.9, 62.5, 47.0, 46.5, 35.6, 34.0, 33.9, 33.1, 31.7, 31.4, 27.2, 23.4, 22.4, 22.2, 22.0; MS (EI) *m/z* 192 (30%, [M+H]$^+$), 150 (100); HRMS (CI) Calcd for $C_{13}H_{22}N$ (M+H) 192.1752; found, 192.1751 ([M+H]$^+$).

3.8.2. 7-Allyl-8-azaspiro[5.6]dodec-2-ene (35). 84% Yield; colorless oil (mixture of diastereomers);† IR ν_{max}/cm^{-1} 3019, 2925, 2854, 1448, 1438, 1152, 992, 913; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.53 (m, 3H), 5.13–5.01 (m, 2H), 3.17–3.02 (m, 1H), 2.58–2.39 (m, 1H), 2.34–2.15 (m, 2H), 2.10–1.22 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 137.5, 127.2, 126.3, 125.9, 125.7, 117.2, 117.0, 67.8, 67.6, 52.3, 50.0, 38.1, 37.8, 35.8, 35.4, 35.1, 34.6, 32.7, 32.6, 31.7, 31.5, 29.7, 27.8, 22.9, 21.9, 21.2, 21.15; MS (EI) *m/z* 205 (20%, [M]$^+$), 164 (100); HRMS Calcd for $C_{14}H_{23}N$ 205.1831; found, 179.1825.

Acknowledgements

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Total synthesis of eurypamides, marine cyclic-isodityrosines from the Palauan sponge *Microciona eurypa*

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Abstract—Total synthesis of eurypamides A, B, and D, **1**, **2**, and **4**, has been successfully accomplished. The $Tl(NO_3)_3$ (TTN) oxidation of the halogenated bisphenols, **14a**, **14b**, **24**, and **43**, effected regio-controlled cyclization to provide the corresponding diaryl ethers, **15a**, **15b**, **25**, and **46**. This investigation revealed a structural revision of eurypamide A as to possess (2″*S*,3″*R*,4″*S*)-configuration (**47**), along with the spectral data of pure **2** and **4**, which were previously characterized in a mixture.

1. Introduction

The isodityrosine-type natural products are known to exhibit antimicrobial, cytotoxic, and enzyme-inhibitory activities. In such cyclic members, as K-13, OF 4949, and vancomycin, the diaryl ether moiety plays an important role to support the stereochemistry of the peptide chains which regulate their biological activities. In this context, we have extensively synthesized these isodityrosine-type natural products employing phenolic oxidation with TTN, as a key step,[1] which can assemble the cyclic structures by production of the diaryl ether linkage in the desired manner. Upon oxidation of **A** with TTN in MeOH, the corresponding product **B** is produced, and the following Zn-reduction afforded the diaryl ether **C** (Fig. 1). In particular, the ether linkage is exclusively constructed at the iodine position.[2]

We initiated the synthesis of eurypamides, as part of our extensive investigation. Among eurypamides A–D, **1**–**4**, isolated from the Palauan sponge, *Microciona eurypa*,[3] **1** consists of isodityrosine and the unprecedented (2″*S*,3″*S*,4″*R*)-dihydroxyarginine unit. The other three congeners were not isolated, and their structures were determined by direct spectroscopic measurement of a mixture. While eurypamide C **3** was synthesized by Itokawa et al.,[4] no synthetic investigation of the others has been reported. In addition, eurypamides might be expected to possess biological activities by their structural similarity to other cyclic isodityrosine-members, although no such information has been reported, to our knowledge. We describe herein the synthesis of eurypamides A, B, and D, **1**, **2**, and **4**.[5]

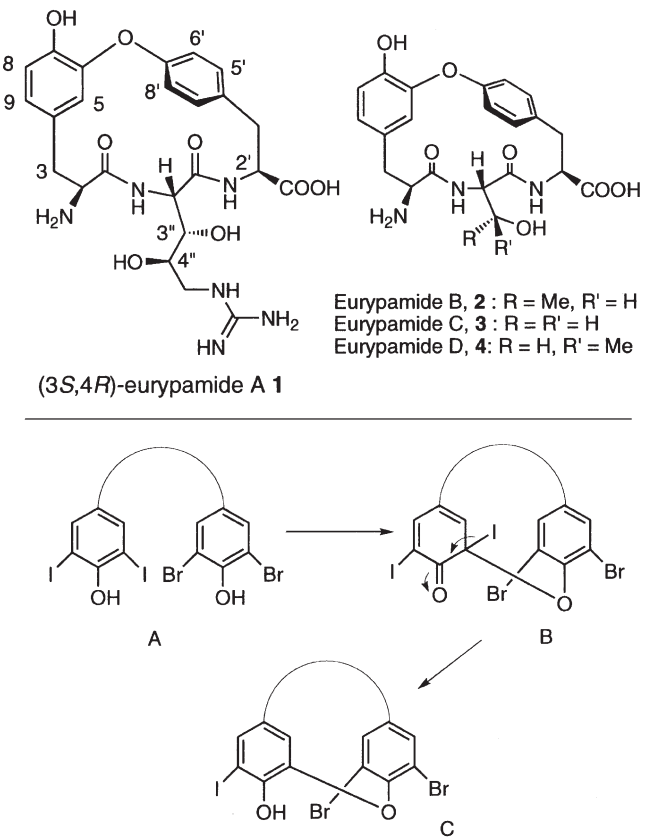

Figure 1.

2. Results and discussion

In our retrosynthetic analysis, the cyclic structure would be constructed by ring-closing at the ether linkage by means of the TTN oxidation of **5** (Scheme 1). The substrate **5** would

Keywords: Eurypamides; Isodityrosine; L-Threonine.
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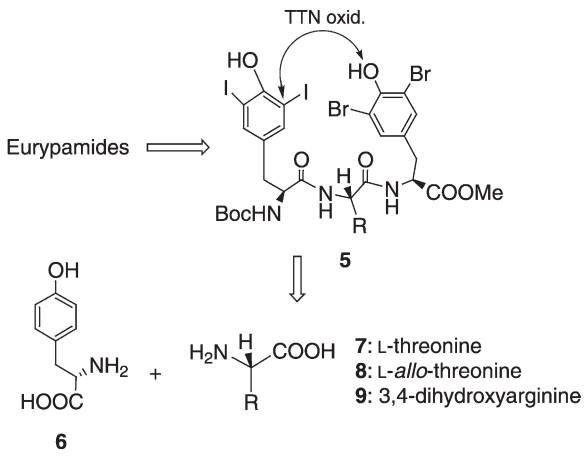


Scheme 1. Retrosynthetic analysis of eurypamides A, B, and D, **1**, **2**, and **4**.

be synthesized from L-tyrosine **6** and, L-threonine **7** for **2**, L-*allo*-threonine **8** for **4**, or (3*S*,4*R*)-dihydroxyarginine unit **9** for **1**, a guanidine group of which would be introduced at the final step.

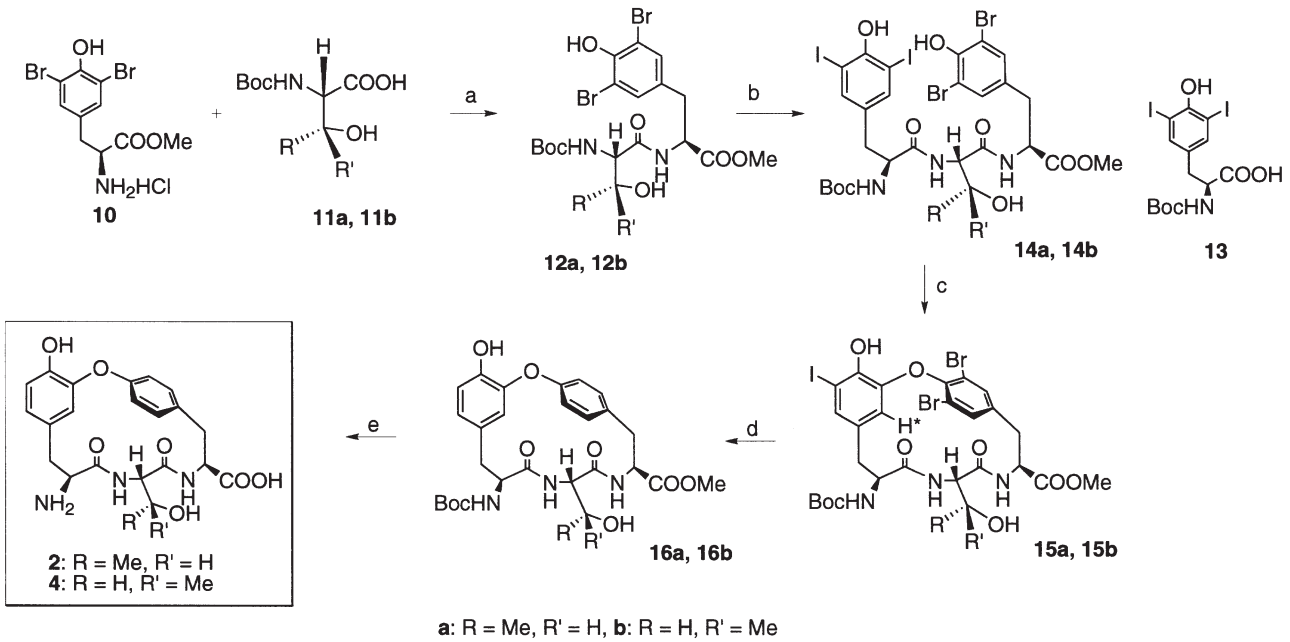
2.1. Synthesis of eurypamide B 2 and D 4

The first synthetic target was the relatively simple eurypamide B **2** to confirm the feasibility of our phenolic oxidation approach employing TTN as an oxidant (Scheme 2). Accordingly, connection of the brominated tyrosine derivative **10**[6] with *N*-Boc-L-threonine **11a** under BOP conditions, provided the dipeptide **12a**. After removal of the Boc group of **12a**, an ammonium salt was further coupled with the diiodotyrosine derivative **13** to give the tripeptide **14a**. TTN oxidation of **14a** in THF–MeOH smoothly proceeded to afford the desired cyclic product **15a** in 72% yield. The structure was determined by the mass and ^{1}H NMR spectra: the high-field shift (δ 5.77) of the aromatic proton signal (*) by the anisotropy effect of another aromatic ring in addition to existence of two Br and one I groups by the mass spectroscopic evidence. Dehalogenation of **15a** was accomplished by Pd-mediated hydrogenolysis, followed by alkaline hydrolysis and TFA treatment to give **2** in good yield. After acid hydrolysis of **2**, gas-chromatographic analysis of the resultant mixture indicated the existence of L-threonine: the phenolic oxidation of **14a** gave rise to cyclization without serious racemization and/or elimination reactions even in the presence of a labile L-threonine.

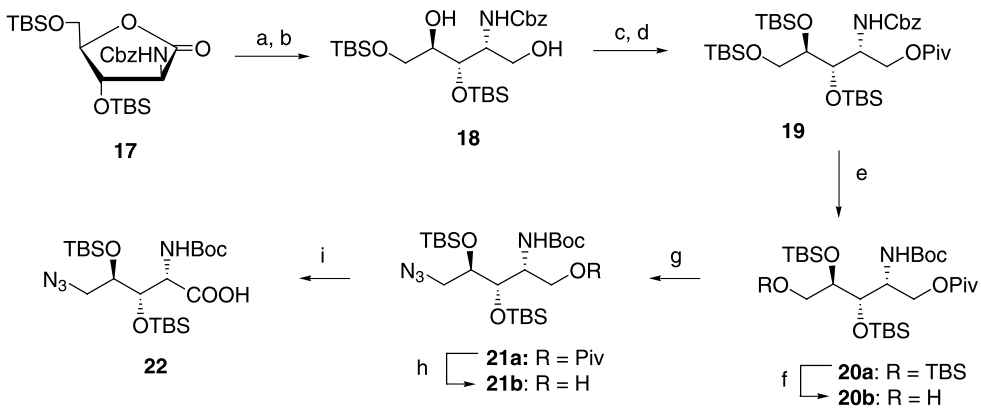
In the next stage, synthesis of eurypamide D **4** was attempted. Tripeptide **14b**, a substrate of the TTN oxidation, was produced essentially as the same procedure as in the case of **14a**, as depicted in Scheme 2. The oxidation of **14b** gave the desired cyclic compound **15b** in 61% yield, which was successively submitted to hydrogenolysis (**16b**), alkaline hydrolysis, and TFA treatment to provide eurypamide D **4**. Based on these successful results, our attention turned to synthesis of eurypamide A **1**.

2.2. Synthesis of eurypamide A 1

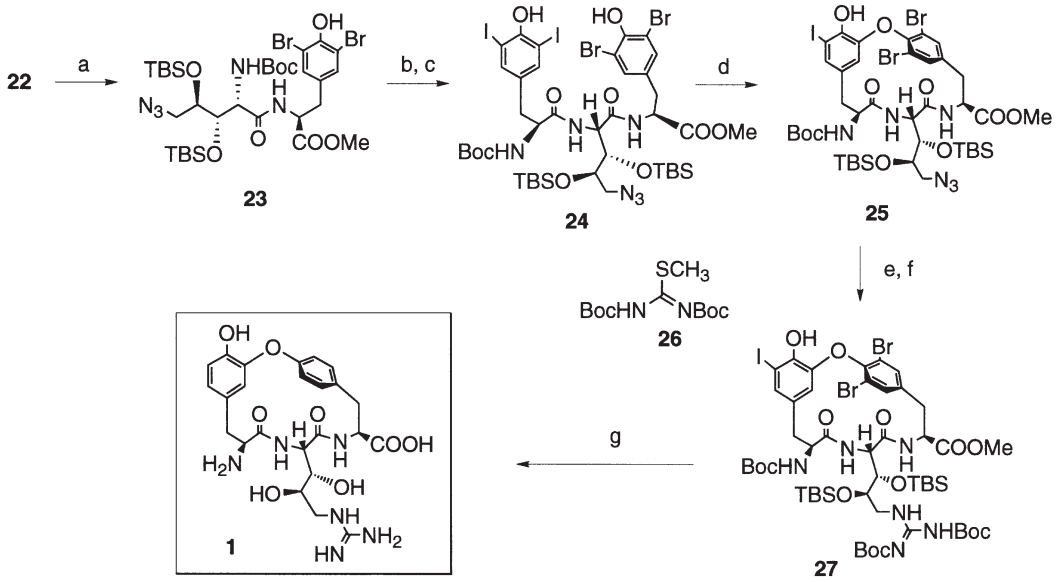
Synthesis of **1** was started from preparation of the (3*S*,4*R*)-dihydroxyarginine derivative. Thus, **17**[7] was produced by condensation of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl isocyanoacetate. Reduction of **17** with DIBAL-H and $NaBH_4$, gave diol **18**. Selective protection of the primary hydroxyl group as a pivaloyl ester, followed by introduction of TBS groups, afforded **19**. After conversion of the Cbz group into the Boc group (**20a**), the primary TBS group was selectively removed (**20b**), followed by azidation (**21a**) and removal of the pivaloyl group to give the primary alcohol **21b**, which on oxidation with TEMPO afforded the amino acid **22** (Scheme 3).



Scheme 2. Reagents and conditions: (a) BOP, Et_3N, DMF: **12a**, 90%; **12b**, 85%. (b) i. TFA, CH_2Cl_2; ii. **13**, BOP, Et_3N, DMF: **14a**, 91% in 2 steps; **14b**, 91% in 2 steps. (c) TTN, THF–MeOH (4:1): **15a**, 72%; **15b**, 61%. (d) H_2, NaOAc, 10% Pd–C, MeOH: **16a**, 100%; **16b**, 100%. (e) i. 1 M aq. NaOH, MeOH, quant; ii. TFA, CH_2Cl_2: **2**, 90% in 2 steps; **4**, 92% in 2 steps.



Scheme 3. Reagents and conditions: (a) DIBAL-H, CH_2C1_2. (b) $NaBH_4$, MeOH, 84% from **21**. (c) PivCl, pyr, 80%. (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 85%. (e) H_2, 10% Pd–C, MeOH; Boc_2O, $NaHCO_3$ aq., dioxane, 100%. (f) PPTS, MeOH, 77%. (g) MsCl, pyr; NaN_3, DMF, 77%. (h) DIBAL-H, CH_2Cl_2, 90%. (i) TEMPO, KBr, NaClO, $NaHCO_3$ aq., acetone, 83%.



Scheme 4. Reagents and conditions: (a) **10**, BOP, Et_3N, DMF, 85%. (b) TFA, CH_2C1_2. (c) **13**, BOP, Et_3N, DMF, 65% in 2 steps. (d) TTN, THF–MeOH (4:1), 63%. (e) Ph_3P, H_2O, THF. (f) $HgCl_2$, Et_3N, DMF, 60% in 2 steps. (g) i. H_2, NaOAc, 10% Pd–C, MeOH; ii. TBAF, THF, 65% in 2 steps; iii. 1 M aq. NaOH, MeOH; iv. TFA, CH_2Cl_2, quant in 2 steps.

Amino acid **22** was connected with **10** to give the dipeptide **23** in 85% yield (Scheme 4). After selective removal of the Boc group, the second coupling with **13** afforded the desired tripeptide **24**. TTN oxidation of **24** effected the cyclization to give the cyclic diaryl ether **25** in 63% yield. Upon monitoring by TLC, there were no remarkable byproducts except highly polar-products, which might be produced by polymerization. The azide group of **25** was selectively reduced, followed by introduction of the guanidine group to give **27**. Removal of the halogen atoms and the TBS groups, followed by successive hydrolysis for the ester and the N-protecting group, gave (3″*S*,4″*R*)-eurypamide A **1**. Comparison of the ^{1}H NMR data of the synthetic sample with those reported (Table 1), indicated a clear difference in the region of the methine protones of the dihydroxyarginine moiety while the respective ^{13}C NMR spectra and optical rotations were similar ($[\alpha]_D^{20}$ −17.8 (*c* 0.23, MeOH), lit.[3] $[\alpha]_D$ −21.5 (*c* 0.23, MeOH)).

Faulkner described that the rigid system of eurypamide A **1** enabled determination of the stereochemistry, with the exception of those at the C-3 and 4 positions.[3] The acetonide derivative of **1** was used to determine the stereochemistry of the C-3 and 4 positions; both H-3 and H-4 showed NOE correlations to the same acetonide-methyl group. This observation revealed that the C-3 and 4 positions should have (3″*S*,4″*R*)- or (3″*R*,4″*S*)-configuration. Although they adopted a more energetically preferred (3″*S*,4″*R*)-configuration in the molecular modeling calculation, we expected **1** might possess a more labile (3″*R*,4″*S*)-stereochemistry. Based on this working-hypothesis, the corresponding arginine derivative carrying (3″*R*,4″*S*)-configuration was synthesized from D-ribose.

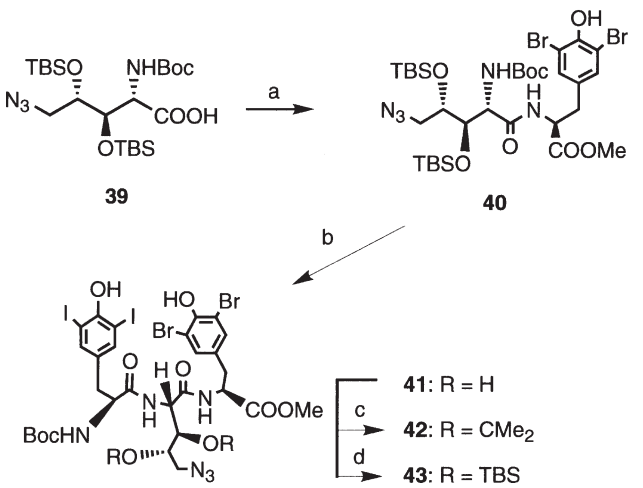
2.3. Synthesis of (3″*R*,4″*S*)-eurypamide A 47

Introduction of an azide group at the free hydroxyl group position of **28**[8] under the Mitsunobu conditions provided **29** (Scheme 5). Reduction of the azide and successive Boc protection afforded **30**. Debenzylation (**31**) and selective

Table 1. Comparison of the ^{1}H NMR data (CD_3OD) of the synthetic **1** with the reported data (Ref. 3)

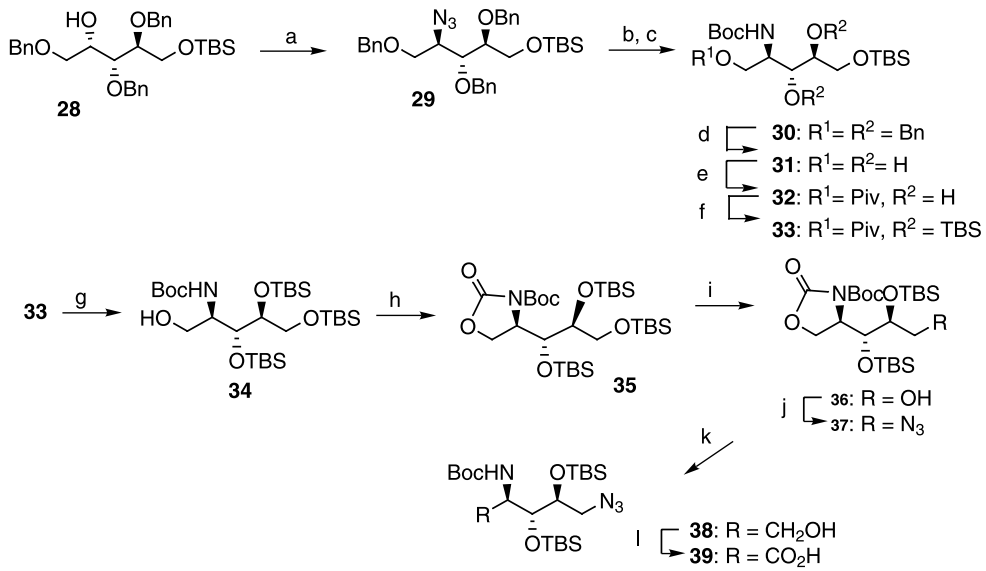
	Synthetic 1		Natural data (ref. 3)	
H	δ_H		δ_H	
3'	2.71	1H, t, 12.7	2.70	1H, t, 12.5
3	2.95	1H, dd, 5, 15	2.98	1H, dd, 6, 15
3	3.20	1H, d, 13	3.20	1H, d, 15
3'			3.35	1H, dd, 7, 12.5
3'	3.32	1H [a)]	3.46	1H, dd, 3, 12.5
5"	3.43-3.52	3H, complex	3.47	1H, dd, 2, 12.5
3"			3.70	1H, dd, 4.5, 8
4"	3.93	1H, dd, 2, 9	3.87	1H, ddd, 2, 7, 8
2	4.20	1H, m	4.15	1H, d, 6
2"	4.75	1H, m	4.70	1H, d, 4.5
2'	4.85	1H, m	4.78	1H, dd, 3, 12.5
5	5.91	1H, d, 2	5.95	1H, d, 2
9	6.67	1H, dd, 2, 8	6.68	1H, dd, 2, 8
8	6.84	1H, d, 8	6.85	1H, d, 8
8'	6.87	1H, dd, 2, 8	6.89	1H, dd, 2, 8
6'	7.03	1H, dd, 2, 8	7.05	1H, dd, 2, 8
9'	7.22	1H, dd, 2, 8	7.22	1H, dd, 2, 8
5'	7.42	1H, dd, 2, 8	7.43	1H, dd, 2, 8

protection with a pivaloyl (**32**) and TBS groups, gave **33**. After selective removal of the primary TBS group, an alcohol generated was submitted to mesylation and azidation. However, the required substitution did not proceed. Based on our working-hypothesis of influence of the amide proton, protection of the amide proton would effect the desired introduction of an azide group. Thus, after removal of the pivaloyl group of **33**, alcohol **34** was treated with NaH, followed by Boc protection to give the oxazolidinone **35**. The primary TBS ether was selectively removed (**36**), followed by successive mesylation and azidation to give the desired **37**. Hydrolysis of the oxazolidinone proceeded under Cs_2CO_3 conditions, and the resulted primary alcohol (**38**) was oxidized with TEMPO to give the amino acid **39**.

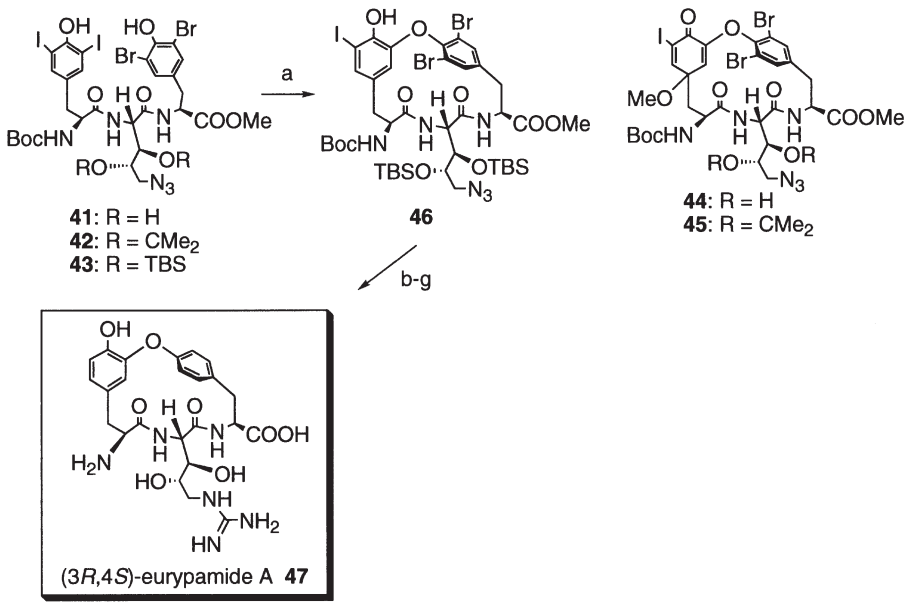


Scheme 6. Reagents and conditions: (a) **10**, BOP, Et_3N, DMF, 81%. (b) i. TBAF, THF; ii. TFA, CH_2C1_2, **13**, EDC, HOBt, Et_3N, DMF, 85% in 3 steps. (c) 2,2-dimethoxypropane, cat. TsOH, DMF, 47%. (d) i. TBSOTf, 2,6-lutidine, CH_2Cl_2; ii. K_2CO_3, MeOH, 60%.

Amino acid **39** was coupled with **10** to give dipeptide **40** (Scheme 6). After deprotection of the Boc group, coupling reaction with **13** was attempted. Unfortunately, no expected product was obtained under several reaction conditions. Accordingly, the TBS and Boc groups of **40** were removed, and the resulting amino alcohol was submitted to coupling with **13** to give tripeptide **41** in good yield. To examine



Scheme 5. Reagents and conditions: (a) Ph_3P, DEAD, DPPA, THF, 92%. (b) Ph_3P, H_2O, THF. (c) Boc_2O, $NaHCO_3$, H_2O–dioxane, 92% in 2 steps. (d) H_2, 10% Pd–C, EtOH. (e) PivCl, pyr., 66% in 2 steps. (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%. (g) DIBAL-H, CH_2Cl_2, 92%. (h) i. NaH, THF, 93%; ii. Boc_2O, DMAP, Et_3N, THF, 86%. (i) CSA, MeOH, 67%. (j) i. MsCl, pyr.; ii. NaN_3, DMF, 80%. (k) Cs_2CO_3, MeOH, 85%. (l) TEMPO, KBr, NaClO, $NaHCO_3$ aq., acetone, 85%.



Scheme 7. Reagents and conditions: (a) TTN, THF–MeOH (4:1), **44**: 56%, **45**: 47%, **46**: 56%. (b) i. Ph_3P, H_2O, THF; ii. $HgCl_2$, Et_3N, DMF, 72%; iii. H_2, NaOAc, 10% Pd–C, MeOH, quant; iv. TBAF, THF, 70%; v. 1 M aq. NaOH, MeOH, quant; vi. TFA, CH_2Cl_2, quant.

adaptability to the TTN cyclization, acetonide **42** and TBS derivative **43** were produced from **41**. Among the oxidation reactions of **41**, **42** and **43**, **41** and **42** provided not the desired cyclic isodityrosine but the spirodienone-type compounds **44** and **45** in moderate yields, while the TBS derivative **43** provided the desired product **46** in 56% yield. Compound **46** in hand was derivatized by essentially the same procedure as in the case of **24** to afford (3″*R*,4″*S*)-eurypamide A **47** (Scheme 7). Under the full range of spectroscopic data, the synthetic sample was superimposable to those of the reported data.

3. Conclusion

Eurypamides A **1**, B **2**, and D **4**, were successfully synthesized by employing the TTN-mediated oxidative cyclization of the corresponding phenols **14a**, **14b**, **24**, and **43**. In addition to supplying the spectroscopic data of pure **2** and **4**, structural revision of **1** was accomplished: the dihydroxyarginine residue of **1** possesses (2″*S*,3″*R*,4″*S*)-configuration **47**.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere unless otherwise noted. Optical rotations were measured on a Jasco DIR-360 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a Jasco Model A-202 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained on JNM-EX270 and JNM-GX400 spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard, as otherwise stated. High-resolution mass spectra were obtained on a Hitachi M-80B GC-MS spectrometer operating at the ionization energy of 70 eV or JEOL JMS-700 (FAB) spectrometers. Preparative and analytical TLCs were carried out on silica gel plate (Kieselgel 60 PF_{254}, E. Merck AG. Germany) using UV light and 5% molybdophosphoric acid in ethanol or 2% ninhydrin in 1-propanol for detection. Kanto Chemical silica 60 N (spherical, neutral, 63–210 μm) was used for column chromatography.

4.2. Synthesis of eurypamide B 2 and D 4

4.2.1. *N*-*tert*-Butoxycarbonyl-L-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 12a. A mixture of **11a** (1.83 g, 8.4 mmol), **10** (3.63 g, 8.4 mmol), BOP reagent (3.69 g, 8.35 mmol), and Et_3N (2 mL, 15 mmol) in DMF (17 mL) was stirred overnight. After the addition of 5% $KHSO_4$ aq., the mixture was extracted with EtOAc, then washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (1/1 hexane/EtOAc) to give **12a** as an oil (4.15 g, 90%): IR (film) 3392, 1662, 1477, 1367, 1241, 1162 cm^{-1}; δ_H 1.20 (3H, d, *J*=6.4 Hz), 1.45 (9H, s), 2.90 (1H, s), 2.93 (1H, dd, *J*=5.6, 14 Hz), 3.09 (1H, dd, *J*=5.6, 14 Hz), 3.76 (3H, s), 4.05 (1H, m), 4.39 (1H, m), 4.75 (1H, m), 5.43 (1H, d, *J*=8.1 Hz), 5.92 (1H, s), 7.12 (1H, d, *J*=7.3 Hz), 7.24 (2H, s); δ_C 18.4, 28.3, 36.3, 52.6, 53.3, 58.3, 66.8, 80.5, 109.9, 130.2, 132.6, 148.5, 156.2, 171.0; HREIMS *m*/*z* 553.0159, calcd for $C_{19}H_{27}{}^{79}Br_2N_2O_7$ (M^++H) 553.0185.

4.2.2. *N*-*tert*-Butoxycarbonyl-*o*,*o*′-diiodo-L-tyrosyl-L-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 14a. A solution of **12a** (524 mg, 0.94 mmol) in TFA (2 mL)–CH_2Cl_2 (6 mL) was stirred at 0 °C for 3 h. After evaporation, the residue was dissolved in DMF (0.6 mL), containing **13** (504.2 mg, 0.94 mmol), BOP reagent (418 mg, 0.94 mmol) and Et_3N (0.27 mL, 1.9 mmol) were added at 0 °C. After being stirred overnight, the reaction was quenched by the addition of 5% $KHSO_4$ aq., extracted with

EtOAc, and washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (2/3 hexane/EtOAc) to give **14a** as an amorphous solid (850 mg, 91% in 2 steps): $[\alpha]_D^{20}$ +4.2 (*c* 1.00, $CHCl_3$); IR (film) 3388, 1650, 1519, 1477, 1457, 1241, 1160 cm^{-1}; δ_H 1.10 (3H, d, *J*=6.8 Hz), 1.43 (9H, s), 2.94 (2H, complex), 3.05 (1H, dd, *J*=5.6, 14 Hz), 3.75 (3H, s), 4.31 (3H, complex), 4.72 (1H, m), 4.96 (1H, d, *J*=7.6 Hz), 5.72 (1H, s), 5.96 (1H, s), 6.96 (1H, d, *J*=7.6 Hz), 7.14 (1H, d, *J*=7.8 Hz), 7.24 (2H, s), 7.51 (2H, s); δ_C 19.8, 28.7, 36.8, 36.9, 52.8, 55.1, 56.3, 57.1, 59.7, 68.5, 80.9, 85.1, 112.0, 131.9, 134.0, 134.6, 141.4, 151.1, 155.3, 157.6, 171.9, 172.7, 173.7; HRFABMS *m/z* 967.8734, calcd for $C_{28}H_{34}{}^{79}Br_2I_2N_3O_9$ (M^++H) 967.8751. Found: C, 34.75; H, 3.68; N, 4.22. Calcd for $C_{28}H_{33}Br_2I_2N_3O_9$: C, 34.70; H, 3.43; N, 4.34.

4.2.3. Cyclic tripeptide 15a. To a solution of **14a** (329.2 mg, 0.34 mmol) in THF (140 mL) and MeOH (35 mL) was added TTN (420 mg, 1.0 mmol) at 0 °C. After being stirred for 1 h, Na_2SO_3 and H_2O (1drop) were added. The mixture was passed through a Celite pad, and evaporated to give a residue. Purification by silica-gel column chromatography (1/2 hexane/EtOAc) gave **15a** as an oil (206.6 mg, 72%): $[\alpha]_D^{20}$ +6.5 (*c* 1.00, $CHCl_3$); IR (film) 3332, 1654, 1490, 1455, 1276, 1253, 1172 cm^{-1}; δ_H 1.00 (3H, d, *J*=6.4 Hz), 1.49 (9H, s), 2.57 (1H, t, *J*=12.8 Hz), 2.72 (1H, d, *J*=12.4 Hz), 3.19 (1H, dd, *J*=4.8, 13.2 Hz), 3.35 (1H, dd, *J*=4.0, 13.2 Hz), 3.62 (1H, m), 3.85 (3H, s), 4.05 (1H, m), 4.37 (1H, m), 4.51 (1H, m), 5.01 (1H, m), 5.46 (1H, d, *J*=7.2 Hz), 5.75 (1H, d, *J*=2 Hz), 6.32 (1H, s), 6.71 (1H, d, *J*=7.6 Hz), 7.06 (1H, d, *J*=1.6 Hz), 7.36 (1H, d, *J*=1.6 Hz), 7.56 (1H, d, *J*=9.6 Hz), 7.66 (1H, s); δ_C 17.2, 28.5, 37.0, 38.8, 52.7, 53.0, 53.7, 56.2, 56.2, 67.7, 79.8, 82.7, 113.5, 116.8, 128.9, 133.8, 134.3, 135.0, 137.0, 142.8, 146.9, 155.0, 168.4, 169.2; HRFABMS *m/z* 841.9602, calcd for $C_{28}H_{33}{}^{79}Br^{81}BrIN_3O_9$ (M^++H) 841.9608.

4.2.4. *N-tert*-Butoxycarbonyl-eurypamide B methyl ester 16a. A solution of **15a** (90.6 mg, 0.11 mmol) in MeOH (1 mL) containing catalytic amounts of 10% Pd/C and NaOAc (26.5 mg, 0.32 mmol) was stirred overnight at ambient temperature in a hydrogen atmosphere. After filtration, the filtrate was evaporated. The residue was purified by silica-gel column chromatography (20/1 $CHCl_3$/MeOH) to give **16a** as an oil (66.3 mg, 100%): $[\alpha]_D^{20}$ +22.4 (*c* 1.00, MeOH); IR (film) 3311, 1654, 1508, 1438, 1367, 1276, 1226, 1166 cm^{-1}; δ_H (CD_3OD) 1.11 (3H, d, *J*=6.4 Hz), 1.42 (9H, s), 2.66 (1H, t, *J*=12.8 Hz), 2.90 (2H, m), 3.29–3.36 (3H, complex), 3.80 (3H, s), 4.06 (1H, m), 4.39 (2H, complex), 4.80 (1H, m), 5.37 (1H, d, *J*=8.4 Hz), 5.88 (1H, d, *J*=1.6 Hz), 6.52 (1H, dd, *J*=2.4, 8.4 Hz), 6.76 (1H, d, *J*=8.4 Hz), 6.87 (1H, dd, *J*=2.4, 8.4 Hz), 7.01 (1H, dd, *J*=2.4, 8.4 Hz), 7.17 (1H, dd, *J*=2.4, 8.4 Hz), 7.37 (1H, dd, *J*=2.4, 8.4 Hz), 7.85 (1H, d, *J*=9.6 Hz), 8.33 (1H, d, *J*=10.4 Hz); δ_C (CD_3OD) 19.7, 28.7, 38.3, 39.5, 52.9, 54.7, 54.9, 58.6, 69.6, 80.7, 116.5, 117.1, 122.7, 123.4, 124.7, 127.9, 131.6, 133.1, 135.0, 146.3, 149.2, 155.3, 156.9, 170.9, 172.2, 173.0; HRFABMS *m/z* 558.2467, calcd for $C_{28}H_{36}N_3O_9$ (M^++H) 558.2451.

4.2.5. Eurypamide B 2. A solution of **16a** (17 mg, 0.03 mmol) in MeOH (0.5 mL)–1 M NaOH aq. (0.5 mL) at 0 °C was stirred for 30 min. After treatment with Amberlite IR 120B (H^+), evaporation gave a residue, which was dissolved in CH_2Cl_2 (1 mL)–TFA (1 mL). After being stirred at 0 °C for 2 h, the mixture was evaporated to give **2** as an oil (12 mg, 90%): $[\alpha]_D^{20}$ −22.1 (*c* 1.00, MeOH); IR (film) 3407, 1653, 1508, 1384, 1220 cm^{-1}; δ_H (CD_3OD) 1.14 (3H, d, *J*=6.4 Hz), 2.66 (1H, t, *J*=13 Hz), 2.93 (1H, dd, *J*=5, 15 Hz), 3.20 (1H, broad d, *J*=15 Hz), 3.42 (1H, dd, *J*=4, 13 Hz), 4.16 (2H, complex), 4.43 (1H, d, *J*=2.4 Hz), 4.72 (1H, dd, *J*=4, 13 Hz), 5.94 (1H, d, *J*=2 Hz), 6.65 (1H, d, *J*=2, 8 Hz), 6.83 (1H, d, *J*=8 Hz), 6.86 (1H, d, *J*=2, 8 Hz), 7.02 (1H, dd, *J*=2, 8 Hz), 7.19 (1H, d, *J*=2, 8 Hz), 7.41 (1H, d, *J*=2, 8 Hz); δ_C (CD_3OD) 19.9, 36.9, 39.8, 53.9, 58.7, 58.8, 69.5, 116.7, 117.0, 122.7, 123.4, 124.5, 124.9, 131.8, 133.0, 135.7, 147.2, 149.7, 154.8, 168.4, 168.5, 170.7; HRFABMS *m/z* 444.1758, calcd for $C_{22}H_{26}N_3O_7$ (M^++H) 444.1771.

4.2.6. Chiral GC analysis of eurypamide B 2. Compound **2** (1 mg) in 6 M aq. HCl was heated at 120 °C overnight in the sealed tube. After evaporation, the residue was heated in HCl/MeOH for 1 h. The mixture was then evaporated, and the residue was treated with trifluoroacetic anhydride (0.5 mL) for 1 h under the same conditions. The mixture was evaporated, and the residue was dissolved in Et_2O (0.5 mL). The resulting solution was submitted to Chiral GC analysis using Chirasil–Val column (25 m×0.25 mm; the program rate: 50 °C (10 min), then 50–200 °C at 4 °C/min). The GC analysis for the amino acids established the presence of L-threonine (19.48 min).

4.2.7. *N-tert*-Butoxycarbonyl-L-*allo*-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 12b. A mixture of **11b** (65.2 mg, 0.3 mmol), **10** (129 mg, 0.3 mmol), BOP reagent (132 mg, 0.3 mmol), and Et_3N (0.084 mL, 0.6 mmol) in DMF (2 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (1/1 hexane/EtOAc) gave **12b** as an oil (140.1 mg, 85%): IR (film) 3382, 1658, 1479, 1241, 1160 cm^{-1}; δ_H 1.26 (3H, d, *J*=6.4 Hz), 1.44 (9H, s), 2.96 (1H, dd, *J*=6.8, 14 Hz), 3.06 (1H, dd, *J*=5.2, 14 Hz), 3.71 (1H, m), 3.73 (3H, s), 3.93 (1H, m), 4.05 (1H, m), 4.78 (1H, m), 5.53 (1H, d, *J*=8.0 Hz), 6.25 (1H, s), 7.06 (1H, d, *J*=7.6 Hz), 7.28 (2H, s); δ_C 19.8, 28.3, 36.2, 52.6, 52.7, 53.3, 58.5, 69.2, 76.6, 76.9, 77.2, 77.3, 80.5, 109.9, 130.3, 132.6, 148.6, 156.1, 171.1, 171.2; HREIMS *m/z* 553.0223, calcd for $C_{19}H_{27}{}^{79}Br_2N_2O_7$ (M^++H) 553.0185.

4.2.8. *N-tert*-Butoxycarbonyl-*o*,*o*′-diiodo-L-tyrosyl-L-*allo*-threonyl-*o*,*o*′-dibromo-L-tyrosine methyl ester 14b. To a solution of **12b** (213.3 mg, 0.385 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (1.5 mL) at 0 °C. After being stirred for 1 h, the mixture was concentrated in vacuo. The residue was dissolved in DMF (3 mL), **13** (250 mg, 0.46 mmol), EDC (82.6 mg, 0.43 mmol), HOBt (70.6 mg, 0.43 mmol), and Et_3N (0.1 mL, 0.71 mmol) were added at 0 °C; the mixture was stirred overnight. Work-up and purification by silica-gel column chromatography (2/3 hexane/acetone) gave **14b** as an oil (340.4 mg, 91% in 2 steps): $[\alpha]_D^{20}$ +1.5 (*c* 1.00, MeOH); IR (film) 3361, 1564 cm^{-1}; δ_H (CD_3OD) 1.16 (3H, d, *J*=6.4 Hz), 1.38 (9H, s), 2.64 (1H, dd, *J*=10, 14 Hz), 2.94 (2H, complex),

3.04 (1H, dd, *J*=6.0, 14 Hz), 3.70 (3H, s), 3.97 (1H, m), 4.24 (1H, dd, *J*=6.0, 10 Hz), 4.33 (1H, d, *J*=6.4 Hz), 4.65 (1H, m), 7.34 (2H, s), 7.62 (2H, s); δ_C (CD_3OD) 19.7, 28.6, 28.7, 36.9, 37.0, 52.8, 55.2, 57.0, 59.8, 68.9, 80.8, 85.1, 112.0, 132.0, 134.1, 134.6, 141.4, 151.1, 155.4, 157.6, 171.7, 172.8, 173.6; HRFABMS *m/z* 969.8769, calcd for $C_{28}H_{34}{}^{79}Br^{81}BrI_2N_3O_9$ (M^++H) 969.8731.

4.2.9. Cyclic tripeptide 15b. To a solution of **14b** (95.7 mg, 0.1 mmol) in THF (40 mL) and MeOH (10 mL) was added TTN (110 mg, 0.24 mmol) at 0 °C. After being stirred for 1 h, the reaction was quenched by the addition of Na_2SO_3 and H_2O (1drop). The mixture was passed through a Celite pad, and evaporated. The residue was purified by silica-gel column chromatography (10/1 $CHCl_3$/MeOH) to give **15b** as an amorphous solid (50.9 mg, 61%): $[\alpha]_D^{20}$ +3.6 (*c* 1.00, $CHCl_3$); IR (film) 3332, 1656, 1490, 1455, 1421, 1367, 1253, 1170 cm^{-1}; δ_H 1.11 (3H, d, *J*=6.0 Hz), 1.44 (9H, s), 2.62 (2H, complex), 3.15 (1H, dd, *J*=6.4, 13 Hz), 3.36 (1H, dd, *J*=4.0, 13 Hz), 3.81 (3H, s), 4.39 (1H, m), 4.49 (1H, m), 4.97 (1H, m), 5.41 (1H, d, *J*=7.2 Hz), 5.66 (1H, s), 6.49 (1H, broad), 6.87 (1H, d, *J*=8 Hz), 7.05 (1H, broad s), 7.40 (1H, d, *J*=2 Hz), 7.58 (1 h, d, *J*=9 Hz), 7.64 (1H, broad s); δ_C 18.4, 19.5, 28.5, 36.8, 38.1, 52.9, 53.0, 53.5, 56.7, 58.4, 69.2, 79.8, 82.7, 113.5, 117.1, 118.5, 129.0, 133.4, 134.2, 134.9, 137.0, 142.8, 144.0, 146.9, 155.0, 169.1, 169.9, 171.1, 171.3; HRFABMS *m/z* 839.9646, calcd for $C_{28}H_{33}{}^{79}Br_2IN_3O_9$ (M^++H) 839.9628.

4.2.10. *N-tert*-Butoxycarbonyl-eurypamide D methyl ester 16b. A solution of **15b** (26 mg, 0.031 mmol) in MeOH (1 mL) containing catalytic amounts of 10% Pd/C and NaOAc (7.6 mg, 0.093 mmol) was stirred at ambient temperature overnight in a hydrogen atmosphere. Work-up and purification by silica-gel column chromatography (10/1 $CHCl_3$/MeOH) gave **16b** as an oil (21.1 mg, 100%): $[\alpha]_D^{20}$ +14.9 (*c* 1.00, MeOH); IR (film) 3419, 1656, 1508, 1438, 1367, 1276, 1226, 1166 cm^{-1}; δ_H (CD_3OD) 1.12 (3H, d, *J*=6.4 Hz), 1.43 (9H, s), 2.68 (1H, t, *J*=12.4 Hz), 2.85 (1H, d, *J*=14 Hz), 2.95 (1H, dd, *J*=7, 14 Hz), 3.34 (1H, dd, *J*=4, 13 Hz), 3.79 (3H, s), 3.92 (1H, m), 4.34 (1H, m), 4.44 (1H, m), 4.79 (1H, dd, *J*=4, 13 Hz) 5.46 (1H, d, *J*=8.4 Hz), 5.87 (1H, d, *J*=1.6 Hz), 6.53 (1H, dd, *J*=2.4, 8.4 Hz), 6.76 (1H, d, *J*=8 Hz), 6.88 (1H, dd, *J*=2.4, 8.4 Hz), 7.01 (1H, dd, *J*=2.4, 8.4 Hz), 7.19 (1H, dd, *J*=2.4, 8.4 Hz), 7.35 (1H, dd, *J*=1.6, 8 Hz), 7.95 (1H, d, *J*=9.2 Hz); δ_C (CD_3OD) 19.1, 28.7, 38.1, 39.1, 52.9, 54.7, 54.8, 55.4, 58.6, 69.5, 80.7, 116.6, 117.1, 119.3, 122.6, 123.3, 124.8, 128.1, 131.3, 133.1, 134.9, 146.4, 155.5, 170.5, 172.2, 172.9; HRFABMS *m/z* 558.2464, calcd for $C_{28}H_{36}N_3O_9$ (M^++H) 558.2451.

4.2.11. Eurypamide D 4. To a solution of **16b** (16.6 mg, 0.03 mmol) in MeOH (0.5 mL) was added 1 M NaOH aq. (0.5 mL) at 0 °C; the mixture was stirred for 30 min. After treatment with Amberlite IR 120B (H^+), evaporation gave a residue, which was dissolved in CH_2Cl_2 (1 mL)–TFA (1 mL) at 0 °C. After being stirred for 2 h, the mixture was evaporated, and the residue was co-evaporated several times with toluene to give **4** as an oil (12 mg, 92%): $[\alpha]_D^{20}$ −21.5 (*c* 1.00, MeOH); IR (film) 3297, 1666, 15081438, 1276, 1208 cm^{-1}; δ_H (CD_3OD) 1.14 (3H, d, *J*=6.4 Hz), 2.69 (1H, t, *J*=12.7 Hz), 2.94 (1H, dd, *J*=6.0, 15 Hz), 3.20 (1H, broad d, *J*=14 Hz), 3.40 (1H, dd, *J*=4.0, 13 Hz), 4.04 (1H, m), 4.09 (1H, m), 4.54 (1H, dd, *J*=6, 10 Hz), 4.75 (1H, m), 5.92 (1H, d, *J*=2 Hz), 6.66 (1H, dd, *J*=2, 8 Hz), 6.83 (1H, d, *J*=8 Hz), 6.88 (1H, dd, *J*=2, 8.4 Hz), 7.02 (1H, dd, *J*=2, 8.4 Hz), 7.22 (1H, dd, *J*=2, 8.4 Hz), 7.39 (1H, dd, *J*=2, 8.4 Hz), 8.20 (1H, d, *J*=10 Hz), 8.38 (1H, d, *J*=10 Hz); δ_C (CD_3OD) 18.9, 36.8, 37.8, 55.1, 58.7, 62.3, 69.2, 116.8, 117.0, 122.7, 123.4, 124.5, 124.9, 128.5, 131.7, 133.1, 135.6, 137.4, 147.2, 149.7, 154.8, 168.5, 176.7; HRFABMS *m/z* 444.1754, calcd for $C_{22}H_{26}N_3O_7$ (M^++H) 444.1771.

4.3. Synthesis of (3*S*,4*R*)-eurypamide A 1

4.3.1. 2-(*N*-Benzyloxycarbonyl)amino-2-deoxy-3,4,5-tri-(*tert*-butyldimethylsilyloxy)-1-pivaloyl-D-arabinitol 19. To a solution of **17** (2.1 g, 4.1 mmol) in CH_2Cl_2 (30 mL) was added DIBAL-H (6 mL, 1 M in toluene) at −78 °C; the mixture was stirred for 1 h. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with Rochelle salt aq. and brine, dried (Na_2SO_4), then evaporated to give a residue, which was dissolved in MeOH (30 mL), and $NaBH_4$ (120 mg, 3 mmol) was added at 0 °C. After being stirred for 30 min at ambient temperature, the resulted mixture was partitioned between EtOAc and H_2O. Work-up and purification by silica-gel column chromatography (3/1 hexane/EtOAc) gave **18** as an oil (1.82 g, 84% in 2 steps): δ_H 0.07–0.16 (12H, complex), 0.90 (18H, s), 1.17 (9H, s), 3.53 (1H, dd, *J*=6.8, 9.6 Hz), 3.68 (1H, m), 3.78 (4H, complex), 4.00 (1H, m), 5.10 (2H, complex), 5.63 (1H, d, *J*=8.8 Hz), 7.35 (5H, complex). This compound was immediately submitted the next step.

To a solution of **18** (421 mg, 0.82 mmol) in CH_2Cl_2 (8 mL) was added pivaloyl chloride (0.5 mL, 4.1 mmol) at 0 °C; the mixture was stirred at ambient temperature for 4 h. The reaction was quenched by the addition of 5% $KHSO_4$ aq., and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ aq. and brine, dried (Na_2SO_4), then evaporated. A mixture of the residue (392 mg, 0.66 mmol), 2,6-lutidine (0.6 mL, 5.2 mmol), and TBDMSOTf (0.6 mL, 2.6 mmol) in CH_2Cl_2 (6 mL) was stirred for 1 h. Work-up and purification by silica-gel column chromatography (20/1 hexane/EtOAc) gave **19** as an amorphous solid (398 mg, 85%): $[\alpha]_D^{20}$ +6.0 (*c* 1.00, $CHCl_3$); IR (film) 1733, 1471, 1255, 1149 cm^{-1}; δ_H 0.04 (3H, s), 0.05 83H, s), 0.06 (6H, s), 0.12 (3H, s), 0.87 (9H, s), 0.89 (9H, s), 0.91 (9H, s), 1.18 (9H, s), 3.55 (1H, dd, *J*=5.6, 11 Hz), 3.64 (1H, dd, *J*=5.2, 11 Hz), 3.71 (1H, m), 3.89 (1H, t, *J*=11 Hz), 3.99 (1H, d, *J*=2.8 Hz), 4.12 (2H, complex), 4.99 (1H, d, *J*=12.8 Hz), 5.12 (1H, d, *J*=12.8 Hz), 5.23 (1H, d, *J*=7.2 Hz), 7.33 (5H, complex); δ_C −5.1, −4.9, −4.7, −4.1, −3.7, 18.2, 18.3, 18.5, 25.8, 26.0, 27.3, 38.8, 50.2, 63.0, 64.7, 66.6, 71.0, 127.9, 128.1, 128.2, 128.3, 136.4, 155.5, 177.8; HREIMS *m/z* 712.4443, calcd for $C_{36}H_{70}NO_7Si_3$ (M^++H) 712.4460.

4.3.2. 2-(*N-tert*-Butoxycarbonyl)amino-2-deoxy-3,4,5-tri-(*tert*-butyldimethylsilyloxy)-1-pivaloyl-D-arabinitol 20a. A solution of **19** (0.8 g, 1.1 mmol) in MeOH (10 mL) containing of catalytic amounts of 10% Pd/C was stirred for 1 h at ambient temperature in a hydrogen atmosphere. The mixture was passed through a Celite pad, and evaporated. A mixture of the residue, $NaHCO_3$ (150 mg, 1.8 mmol), and Boc_2O (0.4 mL, 1.6 mmol) in H_2O (6 mL)–1,4-dioxane (6 mL) was stirred for 1 h. Work-up and purification by

silica-gel column chromatography (20/1 hexane/EtOAc) gave **20a** as an oil (0.77 g, 100%): $[\alpha]_D^{20}$ +1.4 (*c* 1.00, $CHCl_3$); IR (film) 1720, 1482, 1390, 1365, 1282, 1255, 1151 cm^{-1}; δ_H 0.06 (18H, complex), 0.89 (27H, complex), 1.18 (9H, s), 1.45 (9H, s), 3.53–3.71 (3H, complex), 3.84–4.11 (4H, complex), 5.00 (1H, d, *J*=7.2 Hz); δ_C −5.1, −4.9, −3.9, −3.7, 18.2, 18.3, 18.5, 26.1, 27.2, 27.5, 38.7, 49.9, 62.8, 64.8, 71.2, 76.1, 79.1, 154.9, 177.9; HREIMS *m/z* 678.4607, calcd for $C_{33}H_{72}NO_7Si_3$ (M^++H) 678.4616. Found: C, 58.79; H, 10.45; N, 1.97. Calcd for $C_{33}H_{71}NO_7Si_3$: C58.44; H, 10.55; N, 2.07.

4.3.3. 2-(*N*-*tert*-Butoxycarbonyl)amino-2-deoxy-3,4-di-(*tert*-butyldimethylsilyloxy)-1-pivaloyl-D-arabinitol 20b. To a solution of **20a** (760 mg, 1.1 mmol) in MeOH (10 mL) was added a catalytic amount of PPTS at 0 °C; the mixture was stirred overnight. Work-up and purification by silica-gel column chromatography (10/1 hexane/EtOAc) gave **20b** as an oil (640 mg, 77%): $[\alpha]_D^{20}$ +3.2 (*c* 1.00, $CHCl_3$); IR (film) 3450, 2956, 1720, 1482, 1390, 1255, 1155 cm^{-1}; δ_H 0.07–0.18 (12H, complex), 0.90 (18H, complex), 1.18 (9H, s), 1.42 (9H, s), 3.63 (1H, m), 3.69 (3H, complex), 3.89 (2H, complex), 4.07 (2H, complex), 4.88 (1H, d, *J*=7.8 Hz); δ_C −5.0, −4.8, −4.4, −4.2, −4.15, 18.1, 18.4, 25.9, 26.2, 27.2, 28.4, 38.7, 50.0, 62.5, 62.6, 70.7, 73.2, 79.4, 155.0, 177.8; HREIMS *m/z* 564.3778, calcd for $C_{27}H_{58}NO_7Si_2$ (M^++H) 564.3752. Found: C, 57.53; H, 10.07; N, 2.43. Calcd for $C_{27}H_{71}NO_7Si_2$: C, 57.51; H, 10.19; N, 2.48.

4.3.4. Azide 21a. To a solution of **20b** (557 mg, 0.99 mmol) in pyridine (5 mL) was added MsCl (0.1 mL, 1.3 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was partitioned between EtOAc and H_2O, the organic layer was washed with 5% $KHSO_4$ aq., followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. A mixture of the residue and NaN_3 (514 mg, 7.9 mmol) in DMF (3 mL) was heated at 80 °C for 4 h. After being cooled to ambient temperature; the mixture was filtered. The filtrate was partitioned between EtOAc and H_2O, the organic layer was washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. Purification of the residue by a silica gel column (40/1 hexane/EtOAc) gave **21a** as an oil (454 mg, 77%): $[\alpha]_D^{20}$ +13.1 (*c* 1.00, $CHCl_3$); IR (film) 3450, 2102, 1720, 1473, 1253 cm^{-1}; δ_H 0.09 (3H, s), 0.13 (3H, s), 0.15 (6H, s), 0.92 (9H, complex), 0.94 (9H, s), 1.21 (9H, s), 1.43 (9H, s), 3.27 (1H, dd, *J*=4.6, 13 Hz), 3.45 (1H, dd, *J*=3, 13 Hz), 3.79 (1H, m), 3.92 (1H, m), 4.07 (2H, complex), 4.81 (1H, d, *J*=7.6 Hz); δ_C −5.1, −5.0, −3.85, −3.8, 18.1, 18.5, 26.0, 26.3, 27.2, 28.4, 38.8, 49.2, 50.0, 53.4, 62.5, 72.0, 73.1, 79.6, 154.9, 177.8; HREIMS *m/z* 589.3830, calcd for $C_{27}H_{57}N_4O_6Si_2$ (M^++H) 589.3816.

4.3.5. Azide alcohol 21b. To a solution of **21a** (326 mg, 0.55 mmol) in CH_2Cl_2 (4 mL) was added DIBAL-H (2.0 mL, 1 M in toluene) at −78 °C; the mixture was stirred for 1 h. The reaction was quenched by the addition of EtOAc, and the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with Rochelle salt aq., followed by brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica-gel column chromatography (8/1–4/1 hexane/EtOAc) to give **21b** as an oil (252 mg, 90%): $[\alpha]_D^{20}$ +5.2 (*c* 1.0, $CHCl_3$); IR (film) 3446, 2102, 1697, 1496, 1473, 1390, 1367, 1255 cm^{-1}; δ_H 0.11 (3H, s), 0.15 (9H, s), 0.90 (9H, s), 0.93 (9H, s), 1.43 (9H, s), 2.94 (1H, m), 3.31 (1H, dd, *J*=4.8, 13 Hz), 3.45 (1H, dd, *J*=3.6, 13 Hz), 3.56 (1H, m), 3.72–3.81 (3H, complex), 3.93 (1H, dd, *J*=2, 5.2 Hz), 5.12 (1H, d, *J*=7.3 Hz); δ_C −4.9, −4.8, −4.1, −4.0, 18.1, 18.3, 26.0, 26.1, 28.4, 53.5, 53.9, 63.7, 72.1, 73.4, 79.8, 156.5; HREIMS *m/z* 505.3191, calcd for $C_{22}H_{48}N_4O_5Si_2$ (M^++H) 505.3241.

4.3.6. Amino acid 22. To a solution of **21b** (91.7 mg, 0.182 mmol) in acetone (0.5 mL) and 5% $NaHCO_3$ aq. (0.5 mL) were added TEMPO (35.7 mg, 0.20 mmol), KBr (2.8 mg, 0.018 mmol), and 8% NaClO aq. (0.5 mL). After being stirred for 3 h, the reaction was quenched by the addition of 5% $KHSO_4$ aq. The mixture was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried (Na_2SO_4), then evaporated. The residue was purified by silica-gel column chromatography (20/1 hexane/EtOAc and 10/1 $CHCl_3$/MeOH) to give **22** as an oil (78 mg, 83%): IR (film) 2100, 1718, 1471, 1388, 1253 cm^{-1}; δ_H (CD_3OD) 0.07 (3H, s), 0.13 (3H, s), 0.16 (3H, s), 0.17 (3H, s), 0.89 (9H, s), 0.95 (9H, s), 1.43 (9H, s), 3.33 (1H, t, *J*=3.2 Hz), 3.55 (1H, dd, *J*=2.8, 13.2 Hz), 3.83 (1H, dd, *J*=3.6, 6.8 Hz), 4.33 (1H, broad d, *J*=6.8 Hz), 4.40 (1H, d, *J*=9.2 Hz), 5.55 (1H, d, *J*=9.2 Hz); δ_C (CD_3OD) −5.1, −4.4, −4.3, −4.2, −3.4, −3.3, 18.9, 19.1, 26.5, 26.6, 28.7, 54.0, 56.2, 73.7, 74.8, 80.9, 157.7, 174.4; HRFABMS *m/z* 519.3056, calcd for $C_{22}H_{47}N_4O_6Si_2$ (M^++H) 519.3034.

4.3.7. Dipeptide 23. To a solution of **22** (99.2 mg, 0.19 mmol) and **10** (102 mg, 0.22 mmol) in DMF (1.5 mL) were added BOP reagent (92.2 mg, 0.20 mmol) and Et_3N (0.10 mL, 0.68 mmol) at 0 °C, the reaction mixture was stirred overnight. Work-up and purification by silica-gel column chromatography (8/1 hexane/EtOAc) gave **23** as an oil (140.1 mg, 85%): $[\alpha]_D^{20}$ +15.7 (*c* 1.0, $CHCl_3$); IR (film) 3434, 2103, 1671, 1477 cm^{-1}; δ_H 0.05 (3H, s), 0.13 (6H, s), 0.16 (3H, s), 0.83 (9H, s), 0.90 (9H, s), 1.44 (9H, s), 2.95 (2H, complex), 3.28 (1H, dd, *J*=4.4, 12.8 Hz), 3.40 (1H, dd, *J*=3.2, 12.8 Hz), 3.72 (3H, s), 3.75 (1H, m), 4.26 (1H, m), 4.35 (1H, m), 4.76 (1H, m), 5.41 (1H, d, *J*=6.8 Hz), 5.91 (1H, s), 7.13 (1H, d, *J*=7.2 Hz), 7.22 (2H, s); δ_C −5.1, −4.8, −4.6, −3.9, 18.0, 18.1, 25.9, 28.2, 36.8, 52.4, 53.1, 53.3, 55.2, 72.4, 80.3, 100.5, 109.7, 130.6, 132.5, 148.4, 155.8, 170.2, 171.0; HRFABMS *m/z* 852.2023, calcd for $C_{32}H_{56}{}^{79}Br_2N_5O_8Si_2$ (M^++H) 852.2034.

4.3.8. Tripeptide 24. To a solution of **23** (160.4 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL) at 0 °C. After being stirred for 1 h, the mixture was evaporated. A mixture of the residue, **13** (112.3 mg, 0.210 mmol), BOP reagent (90.3 mg, 0.23 mmol) and Et_3N (0.10 mL, 0.71 mmol) in DMF (1.8 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (6/1 hexane/acetone) gave **24** as an oil (155 mg, 65% in 2 steps): $[\alpha]_D^{20}$ +5.1 (*c* 1.00, $CHCl_3$); IR (film) 3390, 2103, 1660, 1253 cm^{-1}; δ_H 0.01 (1H, s), 0.03 (3H, s), 0.11 (3H, s), 0.16 (3H, s), 0.84 (9H, s), 0.89 (9H, s), 1.43 (9H, s), 2.90 (1H, m), 2.93 (1H, dd, *J*=6.8, 13.2 Hz), 3.03 (1H, dd, *J*=6.8, 14 Hz), 3.10 (1H, m), 3.26 (1H, dd, *J*=3.2, 13 Hz),

3.41 (1H, dd, *J*=3.2, 13 Hz), 3.68 (1H, m), 3.73 (3H, s), 4.21 (1H, m), 4.33 (1H, d, *J*=6.8 Hz), 4.54 (1H, dd, *J*=2.4, 7.2 Hz), 4.76 (1H, m), 4.94 (1H, d, *J*=8.0 Hz), 5.71 (1H, s), 5.91 (1H, s), 6.90 (1H, d, *J*=7.8 Hz), 7.10 (1H, d, *J*=7.6 Hz), 7.22 (2H, s), 7.53 (2H, s); δ_C −4.9, −4.6, −3.8, 14.3, 18.0, 18.1, 21.1, 25.9, 26.8, 27.8, 28.3, 36.6, 52.5, 53.0, 53.5, 54.0, 55.7, 60.4, 71.7, 72.3, 80.5, 82.3, 109.9, 117.8, 132.6, 132.7, 140.0, 148.5, 152.5, 169.3, 1708, 171.0; HRFABMS *m/z* 1267.0624, calcd for $C_{41}H_{63}{}^{79}Br_2I_2N_6O_{10}Si_2$ (M^++H) 1267.0600.

4.3.9. Cyclic tripeptide 25. A mixture of **24** (149.5 mg, 0.12 mmol) and TTN (210 mg, 0.47 mmol) in THF (40 mL)–MeOH (10 mL) was stirred at 0 °C for 1 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **25** as an oil (85 mg, 63%): $[\alpha]_D^{20}$ +38.7 (*c* 1.00, $CHCl_3$); IR (film) 2103, 1681, 1486, 1255 cm^{-1}; δ_H −0.04 (3H, s), 0.08 (3H, s), 0.18 (3H, s), 0.37 (3H, s), 0.90 (9H, s), 1.00 (9H, s), 1.50 (9H, s), 2.41 (1H, t, *J*=12.8 Hz), 2.67 (1H, d, *J*=12.8 Hz), 3.23–3.40 (3H, complex), 3.53 (1H, dd, *J*=3.2, 12.8 Hz), 3.86 (3H, s), 3.91 (1H, m), 3.98 (1H, dd, *J*=3.2, 7.6 Hz), 4.27 (1H, m), 4.53 (1H, dd, *J*=2.8, 8.8 Hz), 4.92 (1H, m), 5.41 (1H, d, *J*=6.8 Hz), 5.87 (1H, d, *J*=1.6 Hz), 6.12 (1H, s), 6.18 (1H, d, *J*=8.8 Hz), 7.05 (1H, d, *J*=1.6 Hz), 7.19 (1H, d, *J*=2 Hz), 7.63 (1H, d, *J*=2 Hz); δ_C −5.3, −5.1, −5.0, −4.3, −3.3, 17.9, 18.0, 25.8, 26.2, 28.4, 36.7, 39.6, 52.8, 53.8, 72.5, 73.2, 79.5, 82.2, 114.0, 116.9, 117.3, 118.9, 128.2, 128.9, 133.9, 134.2, 134.3, 136.7, 142.6, 143.9, 147.0, 154.6, 167.5, 168.1, 170.9; HRFABMS *m/z* 1141.1490, calcd for $C_{41}H_{62}{}^{79}Br^{81}BrIN_6O_{10}Si_2$ (M^++H) 1141.1457.

4.3.10. Cyclic tripeptide 27. A mixture of **25** (73.2 mg, 0.064 mmol) and Ph_3P (52.5 mg, 0.2 mmol) in THF (0.7 mL)–H_2O (0.05 mL) was heated at 60 °C for 2 h. After evaporation, the residue was passed through silica-gel short column chromatography (2/1 hexane/$CHCl_3$). A mixture of the product, **26** (27.4 mg, 0.096 mmol) $HgCl_2$ (20.6 mg, 0.08 mmol), and Et_3N (0.03 mL, 0.21 mmol) in DMF (0.6 mL) was stirred at 0 °C for 1 h. Work-up and purification by silica-gel column chromatography (5/1 hexane/EtOAc) gave **27** as an oil (51.4 mg, 60%): δ_H 0.01–0.35 (12H, complex), 0.91 (9H,s), 1.03 (9H, s), 1.45 (27H, complex), 2.41 (1H, t, *J*=12.8 Hz), 2.66 (1H, d, *J*=14.0 Hz), 3.38 (4H, complex), 3.80 (1H, m), 3.83 (3H, s), 4.00 (1H, m), 4.23 (1H, m), 4.52 (1H, m), 4.93 (1H, m), 5.43 (1H, m), 5.92 (1H, s), 6.12 (1H, broad), 6.25 (1H, d, *J*=8.8 Hz), 7.03 (1H, s), 7.19 (1H, s), 7.53 (1H, m), 7.62 (1H, s), 8.55 (1H, d, *J*=7.0 Hz), 11.30 (1H, broad); δ_C −5.7, −5.3, −4.1, −4.0, 17.9, 25.8, 25.9, 26.1, 28.0, 28.3, 28.4, 28.5, 36.2, 39.7, 42.8, 52.8, 52.9, 53.8, 72.3, 72.6, 77.2, 79.0, 79.2, 82.1, 83.3, 113.9, 116.8, 118.8, 128.2, 128.9, 134.0, 134.2, 136.9, 142.6, 143.8, 146.9, 152.8, 154.4, 156.1, 163.2, 168.0, 170.6; HRFABMS *m/z* 1355.2855, calcd for $C_{52}H_{82}{}^{79}Br_2IN_6O_{14}Si_2$ (M^++H) 1355.2839.

4.3.11. Proposed eurypamide A 1. A solution of **27** (49 mg, 0.036 mmol) in MeOH (0.5 mL) containing catalytic amounts of 10% Pd/C and NaOAc (8.8 mg, 0.11 mmol) was stirred at ambient temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad, and evaporated. A mixture of the residue and TBAF (1 M in THF, 0.18 mL) in THF (0.6 mL) was stirred for 30 min. Work-up and purification by preparative TLC (1/2 hexane/EtOAc) gave a methyl ester (19.6 mg, 65%): $[\alpha]_D^{20}$ −23.9 (*c* 1.00, $CHCl_3$); IR (film) 3334, 1725, 1650, 1506, 1367, 1228, 1164 cm^{-1}; δ_H 1.43 (18H, complex), 1.50 (9H, s), 2.56 (1H, t, *J*=12 Hz), 2.83 (1H, dd, *J*=2, 14.4 Hz), 3.04 (1H, dd, *J*=6, 14 Hz), 3.26 (1H, m), 3.38 (1H, dd, *J*=3.6, 12.8 Hz), 3.62 (1H, d, *J*=9.2 Hz), 3.80 (3H, s), 4.42 (1H, m), 4.62 (1H, d, *J*=8.8 Hz), 4.90 (1H, m), 5.10 (1H, d, *J*=8.4 Hz), 5.78 (1H, s), 5.89 (1H, d, *J*=2 Hz), 6.55 (1H, dd, *J*=2, 8 Hz), 6.66 (1H, d, *J*=9.2 Hz), 6.85 (1H, d, *J*=8.0 Hz), 6.86 (1H, dd, *J*=2.4, 8.4 Hz), 6.90 (1H, d, *J*=8.4 Hz), 7.08 (2H, complex), 7.36 (1H, s), 7.40 (1H, dd, *J*=2, 8.0 Hz), 8.61 (1H, m), 11.4 (1H, s); δ_C 28.1, 28.2, 28.4, 37.4, 39.7, 43.3, 52.7, 53.3, 53.7, 53.8, 70.9, 71.1, 77.2, 79.6, 83.7, 114.6, 114.8, 121.5, 123.0, 124.1, 126.7, 128.2, 131.0, 132.0, 133.5, 144.2, 147.2, 152.7, 153.2, 155.1, 157.5, 162.1, 168.1, 171.0, 171.3; HRFABMS *m/z* 845.3948, calcd for $C_{40}H_{57}N_6O_{14}$ (M^++H) 845.3933.

To a solution of the protected **1** (19.6 mg, 0.023 mmol) in MeOH (0.3 mL) was added 1 M NaOH aq. (0.3 mL) at 0 °C. After being stirred for 30 min, the reaction was quenched by the addition of Amberlite IR 120B (H^+) and stirred for 15 min. The mixture was filtered, and the filtrate was evaporated. The residue was diluted with CH_2Cl_2 (0.5 mL), and TFA (0.5 mL) was added to the mixture at 0 °C. After being stirred for 2 h, the mixture was treated with essentially the same procedure as in the case of **2** to give (3*S*,4*R*)-**1** as an oil (15 mg, quant): $[\alpha]_D^{20}$ −17.8 (*c* 0.23, MeOH); IR (film) 3280, 1670, 15081438, 1203 cm^{-1}; δ_C (CD_3OD) 36.9, 39.7, 45.8, 53.9, 55.1, 55.4, 71.4, 74.2, 116.6, 117.1, 122.6, 123.5, 124.5, 124.9, 131.9, 133.0, 135.8, 147.2, 149.7, 154.7, 159.6, 169.3, 170.4, 174.8; HRFABMS *m/z* 531.2178, calcd for $C_{24}H_{31}N_6O_8$ (M^++H) 531.2203.

4.4. Synthesis of (3″*R*,4″*S*)-eurypamide A 47

4.4.1. 4-Azido-4-deoxy-2,3,5-tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-ribitol 29. A mixture of **28** (6.14 g, 11 mmol), Ph_3P (4.48 g, 17 mmol), DPPA (3.5 mL, 17 mmol), and DEAD (7.5 mL, 17 mmol) in THF (80 mL) was stirred at ambient temperature for 2 h. Evaporation and purification by silica-gel column chromatography (15/1 hexane/EtOAc) gave **29** as an oil (5.9 g, 92%): IR (film) 2096, 1455, 1255 cm^{-1}; δ_H 0.05 (6H, s), 0.90 (9H, s), 3.67 (3H, complex), 3.76 (1H, dd, *J*=5.2, 10.8 Hz), 3.89 (1H, dd, *J*=4, 10.8 Hz), 3.97 (1H, m), 4.47 (1H, d, *J*=12 Hz), 4.50 (1H, d, *J*=12 Hz), 4.53 (1H, d, *J*=12 Hz), 4.63 (2H, s), 4.70 (1H, d, *J*=12 Hz), 7.35 (15H, complex); δ_C −5.2, 18.4, 26.0, 62.1, 62.3, 70.0, 72.4, 73.2, 73.9, 78.2, 79.4, 127.5, 127.6, 127.7, 127.9, 128.2, 137.8, 137.9, 138.1; HREIMS *m/z* 562.3121, calcd for $C_{32}H_{43}N_3O_4Si$ (M^++H) 562.3101.

4.4.2. 4-(*N*-*tert*-Butoxycarbonyl)amino-4-deoxy-2,3,5-tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-ribitol 30. A mixture of **29** (1.91 g, 3.4 mmol) and Ph_3P (2.72 g, 10.2 mmol) in THF (30 mL)–H_2O (3 mL) was heated at 60 °C for 2 h. After evaporation, the residue was dissolved in H_2O (10 mL)–1,4-dioxane (30 mL), $NaHCO_3$ (0.87 g, 10.2 mmol) and Boc_2O (1.2 mL, 5.1 mmol) were added at 0 °C. After being stirred for 1 h, the mixture was partitioned

between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by silica-gel column chromatography (50/1–10/1 hexane/EtOAc) to give **30** as an oil (1.99 g, 92%): $[\alpha]_D^{20}$ +3.4 (*c* 1.00, $CHCl_3$); IR (film) 3444, 1716, 1496, 1454, 1365, 1251, 1170 cm^{-1}; δ_H 0.09 (3H, s), 0.10 (3H, s), 0.94 (9H, s), 1.46 (9H, s), 3.54 (1H, d, *J*=4.4, 9.2 Hz), 3.70 (2H, complex), 3.85 (2H, complex), 4.00 (1H, m), 4.11 (1H, s), 4.47 (2H, complex), 4.61 (2H, complex), 4.77 (2H, complex), 5.04 (1H, d, *J*=8.8 Hz), 7.27–7.39 (15H, complex); δ_C −5.3, 18.3, 26.0, 28.4, 50.8, 62.7, 69.3, 72.4, 72.9, 73.5, 78.3, 79.0, 80.5, 100.4, 127.3, 127.4, 127.5, 127.6, 127.8, 128.1, 128.2, 138.1, 138.4, 138.6, 155.3; HREIMS *m/z* 635.3735, calcd for $C_{37}H_{53}NO_6Si$ (M^+) 635.3642.

4.4.3. 4-(*N*-*tert*-Butoxycarbonyl)amino-4-deoxy-1-*O*-*tert*-butyldimethylsilyl-5-*O*-pivaloyl-D-ribitol 32. A solution of **30** (2.18 g, 3.4 mmol) in EtOH (40 mL) containing catalytic amounts of 10% Pd/C was stirred for 30 min at ambient temperature in a hydrogen atmosphere. The reaction mixture was passed through a Celite pad, and evaporated. A mixture of crude **31** and pivaloyl chloride (0.5 mL, 3.83 mmol) in pyridine (15 mL) was stirred at ambient temperature for 1 day. Work-up and purification by silica-gel column chromatography (4/1–1/1 hexane/EtOAc) gave **32** as an oil (1.02 g, 66%): $[\alpha]_D^{20}$ −1.3 (*c* 1.00, $CHCl_3$); IR (film) 3384, 1716, 1508, 1253 cm^{-1}; δ_H 0.10 (6H, s), 0.90 (9H, s), 1.21 (9H, s), 1.43 (9H, s), 2.81 (1H, d, *J*=5.2 Hz), 3.50 (1H, d, *J*=5.6 Hz), 3.68 (2H, complex), 3.85 (2H, complex), 4.02 (1H, m), 4.25 (1H, dd, *J*=4, 11.2 Hz), 4.38 (1H, m), 4.93 (1H, d, *J*=8.8 Hz); δ_C −5.4, 18.3, 25.9, 27.2, 28.4, 38.9, 52.4, 63.6, 64.6, 70.9, 73.7, 79.9, 156.0, 178.5; HREIMS *m/z* 450.2903, calcd for $C_{21}H_{44}NO_7Si$ (M^++H) 450.2896.

4.4.4. 4-(*N*-*tert*-Butoxycarbonyl)amino-4-deoxy-1,2,3-tri-*O*-*tert*-butyldimethylsilyl-5-*O*-pivaloyl-D-ribitol 33. To a solution of **32** (0.82 g, 1.8 mmol) in CH_2Cl_2 (15 mL) was added 2,6-lutidine (1.3 mL, 11 mmol) and TBDMSOTf (1.1 mL, 5.5 mmol) at 0 °C; the mixture was stirred at 0 °C for 1 h. Work-up and purification by silica-gel column chromatography (10/1 hexane/EtOAc) gave **33** as an oil (1.1 g, 89%): $[\alpha]_D^{20}$ +6.1 (*c* 1.0, $CHCl_3$); IR (film) 3376, 1722, 1654, 1500, 1463, 1386, 1365, 1255, 1151 cm^{-1}; δ_H 0.10 (18H, complex), 0.90 (27H, complex), 1.19 (9H, s), 1.41 (9H, s), 3.47 (1H, m), 3.73 (2H, complex), 3.92 (1H, d, *J*=6.8 Hz), 4.09 (1H, m), 4.21 (2H, m), 5.11 (1H, d, *J*=12 Hz); HREIMS *m/z* 678.4587, calcd for $C_{33}H_{72}NO_7Si_3$ (M^++H) 678.4616. Found: C, 58.60; H, 10.38; N, 2.02. Calcd for $C_{33}H_{71}NO_7Si_3$: C58.44; H, 10.55; N, 2.07.

4.4.5. 4-(*N*-*tert*-butoxycarbonyl)amino-4-deoxy-1,2,3-tri-*O*-*tert*-butyldimethylsilyl-D-ribitol 34. A mixture of **33** (1.13 g, 1.7 mmol) DIBAL-H (5 mL, 1 M in toluene) in CH_2Cl_2 (10 mL) was stirred for 2 h at −78 °C. Work-up and purification by silica-gel column chromatography (10/1–4/1 hexane/EtOAc) to give **34** as an oil (0.91 g, 92%): $[\alpha]_D^{20}$ +6.2 (*c* 1.00, $CHCl_3$); IR (film) 3406, 1698 cm^{-1}; δ_H 0.08 (18H, complex), 0.89, (9H, s), 0.90, (9H, s), 0.91 (9H, s), 1.43 (9H, s), 3.01 (1H, m), 3.48 (1H, m), 3.65 (2H, complex), 3.80 (2H, complex), 3.98 (1H, m), 4.05 (1H, s), 5.47 (1H, d, *J*=7.6 Hz); δ_C −5.3, −5.0, −4.6, −4.4, −3.9, 18.2, 18.4, 26.0, 28.4, 53.4, 63.8, 64.3, 75.4, 79.1, 155.2; HREIMS *m/z* 594.4051, calcd for $C_{28}H_{64}NO_6Si_3$ (M^++H) 594.4041.

4.4.6. Oxazolidinone 35. To a solution of **34** (0.84 g, 1.4 mmol) in THF (15 mL) was added NaH (111 mg, 60% dispersion in mineral oil, 2.8 mmol) at 0 °C; the mixture was stirred overnight. The reaction was quenched by the addition of saturated NH_4Cl aq., and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue, Et_3N (0.6 mL, 4.2 mmol), DMAP (catalytic amount), and Boc_2O (0.5 mL, 2.1 mmol) in THF (10 mL) was stirred for 1 h. Work-up and purification by silica-gel column chromatography (8/1 hexane/EtOAc) gave **35** as an oil (0.75 g, 86%): $[\alpha]_D^{20}$ +36.5 (*c* 1.00, $CHCl_3$); IR (film) 1797, 1720 cm^{-1}; δ_H 0.09 (18H, complex), 0.03 (3H, s), 0.90 (9H, s), 0.09 (3H, s), 0.10 (3H, s), 0.87 (9H, s), 0.90 (18H, s), 1.53 (9H, s), 3.45 (1H, dd, *J*=4.8, 10.4 Hz), 3.53 (1H, t, *J*=10.4 Hz), 3.71 (1H, dd, *J*=4.0, 8.4 Hz), 4.15 (1H, t, *J*=8.8 Hz), 4.35 (1H, s), 4.45 (1H, dd, *J*=4.0, 9.2 Hz), 4.65 (1H, dd, *J*=4.0, 8.4 Hz); δ_C −5.33, −5.31, −5.1, −4.8, −4.3, −4.2, 17.8, 18.0, 18.3, 25.9, 26.0, 27.4, 28.0, 55.7, 62.8, 64.1, 71.4, 77.9, 83.5, 85.2, 149.5, 152.5; HREIMS *m/z* 620.3794, calcd for $C_{29}H_{62}NO_7Si_3$ (M^++H) 620.3834.

4.4.7. Alcohol 36. To a solution of **35** (377.4 mg, 0.61 mmol) in MeOH (5 mL) was added catalytic amounts of CSA at 0 °C; the mixture was stirred for 3 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **36** as an oil (206 mg, 67%): $[\alpha]_D^{20}$ +58.9 (*c* 1.00, $CHCl_3$); IR (film) 3502, 1808, 1720, 1654, 1471, 1384, 1371, 1255 cm^{-1}; δ_H 0.04 (3H, s), 0.09 (6H, s), 0.11 (3H, s), 0.89 (9H, s), 0.90 (9H, s), 1.55 (9H, s), 2.21 (1H, dd, *J*=5, 8 Hz), 3.61 (2H, complex), 3.74 (1H, m), 4.18 (1H, t, *J*=12 Hz), 4.34 (1H, d, *J*=3.6 Hz), 4.63 (2H, complex); δ_C −5.0, −4.7, −4.4, −4.3, 17.9, 18.0, 25.8, 28.0, 55.6, 62.2, 63.7, 70.9, 76.0, 84.2, 150.1, 152.0; HREIMS *m/z* 506.2983, calcd for $C_{23}H_{48}NO_7Si_2$ (M^++H) 506.2969.

4.4.8. Azide 37. To a solution of **36** (309 mg, 0.61 mmol) in pyridine (4 mL) was added MsCl (0.1 mL, 1.3 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with 5% $KHSO_4$ aq. and brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and NaN_3 (330 mg, 5.7 mmol) in DMF (1.0 mL) was heated at 70 °C overnight. Work-up and purification by silica-gel column chromatography (6/1 hexane/EtOAc) gave **37** as an oil (254 mg, 80%): $[\alpha]_D^{20}$ +29.0 (*c* 0.50, $CHCl_3$); IR (film) 2103, 1818, 1718, 1654, 1461, 1371, 1326, 1257, 1159, 1093 cm^{-1}; δ_H 0.05 (3H, s), 0.09 (3H, s), 0.11 (3H, s), 0.13 (3H, s), 0.90 (18H, s), 1.55 (9H, s), 3.28 (1H, dd, *J*=4.4, 8.8 Hz), 3.41 (1H, dd, *J*=6.8, 12.8 Hz), 3.72 (1H, m), 4.18 (1H, t, *J*=8.8 Hz), 4.23 (1H, d, *J*=2.4 Hz), 4.51 (1H, dd, *J*=4.4, 8.8 Hz), 4.59 (1H, dd, *J*=4.4, 8.8 Hz); δ C −5.0, −4.5, −4.4, −4.3, 18.0, 25.8, 28.0, 49.9, 53.6, 55.7, 62.1, 71.4, 75.0, 84.0, 149.3; HREIMS *m/z* 531.3054, calcd for $C_{23}H_{47}N_4O_6Si_2$ (M^++H) 531.3034.

4.4.9. Primary alcohol 38. To a solution of **37** (254 mg, 0.48 mmol) in MeOH (4 mL) was added Cs_2CO_3 (catalytic amount) at 0 °C; the mixture was stirred for 6 h. Work-up

and purification by silica-gel column chromatography (5/1–2/1 hexane/EtOAc) gave **38** as an oil (204 mg, 85%): $[\alpha]_D^{20}$ +1.6 (*c* 1.00, $CHCl_3$); IR (film) 3382, 2102, 1652, 1457, 1257, 1056 cm^{-1}; δ_H 0.12 (6H, s), 0.14 (3H, s), 0.15 (3H, s), 0.90 (9H, s), 0.92 (9H, s), 1.44 (9H, s), 2.47 (1H, m), 3.29 (1H, dd, *J*=6.8, 12.8 Hz), 3.54 (1H, dd, *J*=3.2, 12.8 Hz), 3.65 (2H, complex), 3.84 (1H, m), 3.90 (1H, m), 4.02 (1H, m), 5.18 (1H, d, *J*=8.0 Hz); δ_C −5.1, −4.4, −3.9, 18.1, 18.3, 25.9, 26.0, 28.4, 52.6, 53.7, 62.4, 73.9, 76.4, 79.6, 155.4; HREIMS *m/z* 505.3230, calcd for $C_{22}H_{49}N_4O_5Si_2$ (M^++H) 505.3241.

4.4.10. Amino acid 39. To a solution of **38** (204 mg, 0.4 mmol) in acetone (2 mL) and 5% $NaHCO_3$ aq. (1.5 mL) were added TEMPO (catalytic amount), KBr (111.1 mg, 0.93 mmol), and 8% NaClO aq. (1 mL, 1.6 mmol). After being stirred for 4 h, Work-up and purification by silica-gel column chromatography (2/1 hexane/EtOAc–10/1 $CHCl_3$/MeOH) gave **39** as an oil (177.4 mg, 85%): $[\alpha]_D^{20}$ +1.0 (*c* 1.00, MeOH); IR (film) 2102, 1716, 1384, 1367, 1255 cm^{-1}; δ_H (CD_3OD) 0.12 (3H, s), 0.15 (3H, s), 0.17 (3H, s), 0.18 (3H, s), 0.88 (9H, s), 0.95 (9H, s), 1.45 (9H, s), 3.55 (1H, dd, *J*=2.8, 13.2 Hz), 3.98 (1H, m), 4.05 (1H, m), 4.32 (1H, m), 6.59 (1H, dd, *J*=8.8 Hz); δ_C (CD_3OD) −4.8, −4.2, −4.1, −3.8, 19.1, 26.5, 26.6, 28.7, 54.6, 57.7, 74.3, 61.5, 77.4, 80.7, 157.0, 172.9; HRFABMS *m/z* 519.3066, calcd for $C_{22}H_{47}N_4O_6Si_2$ (M^++H) 519.3034.

4.4.11. Dipeptide 40. A mixture of **39** (52.9 mg, 0.1 mmol), **10** (71.8 mg, 0.16 mmol), BOP reagent (66.5 mg, 0.16 mmol), and Et_3N (0.05 mL, 0.34 mmol) in DMF (1.5 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (8/1 hexane/EtOAc) gave **40** as an oil (70.4 mg, 81%): $[\alpha]_D^{20}$ +12.2 (*c* 1.00, $CHCl_3$); δ_H 0.06 (3H, s), 0.12 (3H, s), 0.13 (3H, s), 0.16 (3H, s), 0.84 (9H, s), 0.93 (9H, s), 1.46 (9H, s), 2.99 (2H, complex), 3.17 (1H, dd, *J*=7.2, 12 Hz), 3.44 (1H, dd, *J*=4, 12 Hz), 3.71 (3H, s), 3.86 (1H, m), 4.12 (1H, broad d, *J*=6.4 Hz), 4.23 (1H, t, *J*=7 Hz), 4.72 (1H, dd, *J*=6.4, 14 Hz), 5.68 (1H, d, *J*=8 Hz), 5.85 (1H, s), 6.81 (1H, d, *J*=7.2 Hz), 7.23 (2H, s); δ_C −5.3, −4.7, −4.4, −4.1, 18.1, 25.6, 25.8, 25.9, 26.0, 28.3, 29.7, 37.0, 52.5, 53.3, 53.4, 58.0, 70.4, 74.6, 83.9, 109.8, 130.4, 132.5, 148.5, 169.7, 170.8; HRFABMS *m/z* 854.2011, calcd for $C_{32}H_{56}{}^{79}Br^{81}BrN_5O_8Si_2$ (M^++H) 854.2014.

4.4.12. Tripeptide 41. To a solution of **40** (106.8 mg, 0.13 mmol) in THF (1.5 mL) was added TBAF (1 M in THF, 0.5 mL) at 0 °C; the mixture was stirred for 30 min. The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and TFA (0.8 mL) in CH_2Cl_2 (0.8 mL), was stirred at 0 °C for 30 min, and evaporated. A mixture of the residue, **13** (130.6 mg, 0.25 mmol), EDC (46.2 mg, 0.24 mmol), HOBt (32.9 mg, 0.24 mmol) and Et_3N (0.08 mL, 0.61 mmol) in DMF (1.5 mL) was stirred overnight. Work-up and purification by silica-gel column chromatography (20/1 hexane/EtOAc) gave **41** as an oil (109.4 mg, 85%): $[\alpha]_D^{20}$ +0.4 (*c* 1.00, MeOH); IR (film) 3332, 2100, 1637, 1457, 1245, 1159 cm^{-1}; δ_H (CD_3OD) 1.39 (9H, s), 2.65 (1H, dd, *J*=8.4, 14 Hz), 2.85–2.98 (2H, complex), 3.04 (1H, dd, *J*=6.0, 14 Hz), 3.35 (1H, dd, *J*=6.0, 13.2 Hz), 3.50 (1H, m), 3.71 (3H, s), 3.74 (2H, complex), 4.25 (1H, m), 4.67 (2H, complex), 7.34 (2H, s), 7.63 (2H, s); δ_C (CD_3OD) 28.5, 28.7, 36.9, 52.9, 54.9, 55.0, 55.9, 57.1, 72.4, 73.7, 80.9, 85.1, 85.2, 112.0, 131.9, 134.1, 134.6, 141.3, 141.4, 151.1, 157.6, 170.9, 172.3, 173.4; HRFABMS *m/z* 1038.8856, calcd for $C_{29}H_{35}{}^{79}Br_2I_2N_6O_{10}$ (M^++H) 1038.8871.

4.4.13. Tripeptide 43. To a solution of **41** (30 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (0.10 mL, 0.86 mmol) and TBDMSOTf (0.07 mL, 0.31 mmol) at 0 °C; the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of 5% $KHSO_4$ aq., and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and K_2CO_3 in MeOH (2 mL) was stirred for 2 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **43** as an oil (21.8 mg, 60%): $[\alpha]_D^{20}$ +6.8 (*c* 1.00, $CHCl_3$); IR (film) 3363, 2103, 1662, 1475, 1251, 1160 cm^{-1}; δ_H 0.09 (12H, complex), 0.82 (9H, s), 0.92 (9H, s), 1.44 (9H, s), 2.80 (1H, m), 2.91 (1H, dd, *J*=6.4, 13.2 Hz), 3.05 (2H, complex), 3.27 (1H, dd, *J*=6.8, 13.2 Hz), 3.54 (1H, dd, *J*=5.2, 12 Hz), 3.71 (3H, s), 3.74 (1H, m), 3.79 (1H, m), 4.06 (1H, broad d, *J*=4.4 Hz), 4.28 (1H, m), 4.56 (1H, dd, *J*=6.8, 8.4 Hz), 4.69 (1H, m), 4.84 (1H, d, *J*=7.2 Hz), 5.68 (1H, s), 5.87 (1H, s), 6.76 (1H, d, *J*=8.0 Hz), 7.02 (1H, d, *J*=8.0 Hz), 7.23 (2H, s), 7.53 (2H, s); δ_C −5.0, −4.6, −4.2, −4.1, 18.1, 18.2, 25.8, 26.0, 28.3, 36.9, 52.6, 52.8, 55.9, 73.0, 75.3, 80.8, 82.4, 109.9, 130.6, 132.6, 139.7, 139.8, 148.4, 152.6, 168.5, 170.5, 170.7; HRFABMS *m/z* 1266.0578, calcd for $C_{41}H_{63}{}^{79}Br_2I_2N_6O_{10}Si_2$ (M^++H) 1266.0600.

4.4.14. TTN oxidation of 41. A mixture of **41** (11 mg, 0.01 mmol) and TTN (30 mg, 0.06 mmol) in MeOH (1 mL)–THF (4 mL) was stirred at 0 °C for 4 h. Work-up and purification by preparative TLC (1/3 hexane/EtOAc) gave **44** as an oil (3.4 mg, 33%); δ_H 1.41 (9H, s), 1.98 (1H, broad d, *J*=14 Hz), 2.20 (1H, m), 2.59 (1H, t, *J*=12 Hz), 3.24 (3H, s), 3.85 (3H, s), 5.25 (1H, broad s), 7.34 (1H, broad s), 7.41 (1H, d, *J*=2 Hz), 7.53 (1H, broad s).

4.4.15. TTN oxidation of 42. A mixture of **41** (12.2 mg, 0.01 mmol) and 2,2-dimethoxypropane (0.1 mL) in DMF (0.5 mL) in the presence of catalytic amounts of TsOH was heated at 65 °C for 3.5 h: work-up gave **42** (6 mg, 47%). A mixture of **42** (7.8 mg, 0.007 mmol) and TTN (30 mg, 0.06 mmol) in MeOH (1 mL)–THF (4 mL) was stirred at 0 °C for 1 h. Work-up and purification by preparative TLC (20/1 $CHCl_3$/MeOH) gave **45** as an oil (1.8 mg, 25%); δ_H 1.40 (3H, s), 1.44 (9H, s), 1.66 (3H, s), 3.24 (3H, s), 3.84 (3H, s), 5.19 (1H, d, *J*=2.8 Hz), 6.42 (1H, d, *J*=10 Hz), 7.32 (1H, d, *J*=2 Hz), 7.40 (1H, d, *J*=2.8 Hz), 7.57 (1H, d, *J*=2 Hz).

4.4.16. Cyclic tripeptide 46. To a solution of **43** (57.9 mg, 0.046 mmol) in THF (20 mL) and MeOH (5 mL) was added TTN (57.8 mg, 0.13 mmol) at 0 °C; the mixture was stirred for 1 h. Work-up and purification by silica-gel column chromatography (4/1 hexane/EtOAc) gave **46** as an oil (29.0 mg, 56%): $[\alpha]_D^{20}$ +2.8 (*c* 1.00, $CHCl_3$); IR (film) 3374, 2103, 1671, 1455, 1255, 1106 cm^{-1}; δ_H 0.08 (6H, complex), 0.24 (6H, complex), 0.82 (9H, s), 1.00 (9H, s), 1.49 (9H, s), 2.56 (1H, t, *J*=12.8 Hz), 2.68 (1H, d,

J=12.8 Hz), 3.29 (2H, complex), 3.44 (1H, m), 3.80 (3H, s), 3.84 (2H, complex), 4.31 (1H, m), 4.56 (1H, d, J= 7.6 Hz), 4.99 (1H, m), 5.40 (1H, d, J=6.4 Hz), 5.72 (1H, d, J=1.6 Hz), 6.05 (1H, s), 6.64 (1H, d, J=7.2 Hz), 6.88 (1H, d, J=10 Hz), 7.09 (1H, s), 7.26 (1H, overlapped with solvent signal), 7.58 (1H, d, J=2 Hz); δ_C −4.5, −4.4, −4.0, −3.5, 18.1, 18.4, 25.6, 26.2, 28.4, 28.5, 36.3, 38.6, 52.8, 52.9, 53.8, 75.1, 76.4, 79.6, 82.6, 113.5, 116.9, 118.7, 128.8, 133.6, 134.4, 134.6, 136.9, 143.9, 146.9, 154.8, 166.9, 167.9, 170.7; HRFABMS m/z 1139.1438, calcd for $C_{41}H_{62}{}^{79}Br_2IN_6O_{10}Si_2$ (M^++H) 1139.1409.

4.4.17. (3″*R*,4″*S*)-Eurypamide A 47. To a solution of **46** (58.4 mg, 0.051 mmol) in THF (1 mL) and H_2O (0.1 mL) was added Ph_3P (40.7 mg, 0.2 mmol) at ambient temperature; the mixture was heated at 60 °C for 2 h. After evaporation, the residue was purified by silica-gel short column chromatography (30/1 $CHCl_3$/MeOH). A mixture of an amine, **26** (30.7 mg, 0.11 mmol), Et_3N (0.03 mL, 0.21 mmol), and $HgCl_2$ (28.6 mg, 0.11 mmol) in DMF (1 mL) was stirred at 0 °C for 1 h. The reaction mixture was diluted with EtOAc and H_2O, and filtered through a Celite pad. The filtrate was extracted with EtOAc, washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (0.5 mL), containing catalytic amounts of 10% Pd/C and NaOAc (12.5 mg, 0.153 mmol), and the mixture was stirred at ambient temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad, and evaporated. To the residue in THF (0.6 mL) was added TBAF (1 M in THF, 0.18 mL) at 0 °C. After being stirred for 30 min, the mixture was partitioned between EtOAc and H_2O, and the organic layer was washed with brine. The organic layer was dried (Na_2SO_4), and evaporated. The residue was purified by preparative TLC (1/2 hexane/EtOAc) to give the corresponding methyl ester.

A mixture of the methyl ester (8.8 mg, 0.011 mmol) and 1 M NaOH aq. (0.3 mL) in MeOH (0.3 mL) was stirred at 0 °C for 30 min. After the addition of Amberlite IR 120B (H^+), the mixture was filtered. The filtrate was evaporated to give a residue, which was treated at 0 °C with TFA (0.5 mL) in CH_2Cl_2 (0.5 mL) for 2 h. Evaporation gave **47** as an oil (4.0 mg, 82%): $[\alpha]_D^{20}$ −20.5 (c 0.23, MeOH); IR (film) 3390, 1671, 1506, 1428, 1274, 1203 cm^{-1}; δ_H (CD_3OD) 2.67 (1H, t, J=12.7 Hz), 2.96 (1H, dd, J=6, 15 Hz), 3.20 (1H, d, J=15 Hz), 3.34 (1H, dd, J=6.8, 12.4 Hz), 3.44–3.48 (2H, complex), 3.68 (1H, dd, J=4.5, 8 Hz), 3.85 (1H, m), 4.12 (1H, d, J=6 Hz), 4.70 (1H, d, J=4.5 Hz), 4.74 (1H, dd, J=3, 12 Hz), 5.95 (1H, d, J=2 Hz), 6.67 (1H, dd, J=2, 8 Hz), 6.84 (1H, d, J=8 Hz), 6.88 (1H, dd, J=2, 8 Hz), 7.03 (1H, dd, J=2, 8 Hz), 7.20 (1H, dd, J=2, 8 Hz), 7.42 (1H, dd, J=2, 8 Hz); HRFABMS m/z 531.2180, calcd for $C_{24}H_{31}N_6O_8$ (M^++H) 531.2203.

Acknowledgements

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Application of palladium-catalyzed Pd–aryl/P–aryl exchanges: preparation of functionalized aryl phosphines by phosphination of aryl bromides using triarylphosphines

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Abstract—Palladium-catalyzed Pd–aryl/P–aryl interchange reaction was applied in the synthesis of various functionalized arylphosphines. This phosphination used inexpensive, readily available and air stable triarylphosphines as the phosphinating agents. Broad functional groups were compatible including keto, aldehyde, ester, nitrile, ether, chloride, pyridyl and thiophenyl groups. Halides were found to be good promoter for the rates and yields of the reaction.

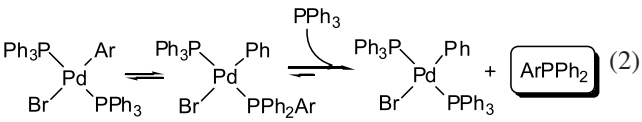
1. Introduction

Cross-coupling reactions are important in organic synthesis, especially in pharmaceutical areas. Palladium-catalyzed coupling methodologies are powerful protocols for carbon–carbon and carbon–heteroatom bond formation.[1] However, some of the undesirable side reactions such as Pd–aryl/P–aryl interchanges were observed when arylphosphine ligands were used (Eq. 1).

X = halides, triflate (1)

The Pd–aryl/P–aryl interchange in forming the scrambled side reaction products have been observed in Suzuki–Miyaura coupling,[2] Stille coupling,[3] Heck reaction,[4,5] amination,[6] amidation,[7] ketone-arylation,[8] cyanation,[9] and C–S bond formation reactions,[10,11] polymer synthesis,[12] and etc.[13] (Scheme 1). Consequently, the yields of the reactions suffer and the purification of products becomes more difficult. The unwanted coupled products usually are obtained from 4 to 58% yield in those couplings (Scheme 1). Furthermore, in polymer synthesis, the architecture of the desired polymer may be altered, possibly resulting in poorer properties.[12]

Cheng,[14] Novak[15] and Grushin[16] have demonstrated this aryl exchange reaction is an equilibrium process. The equilibrium is possibly a fine balance of the electronic and steric nature of the phopshine ligands. Mechanistic studies reveal that electron rich arylphosphines facilitate the Pd–aryl/P–aryl interchange reactions,[15] as the electron-donating group may stabilize the developing positive charge from the phosphonium salt intermediate (see Scheme 2, proposed mechanism). From these results, we utilized the aryl–aryl exchange reactions in the preparation of functionalized aryldiphenylphosphine ($ArPPh_2$) from aryl bromides and triphenylphosphine in the presence of palladium catalyst (Eq. 2).



(2)

Synthesis of functionalized aromatic phosphines for the application in fine-tuning catalysis is highly desirable. However synthetic methods available are limited in scope. Traditional methods for the preparation of aromatic phosphines can be classified into two major categories. One method involves the reaction of aryl Grignard or organolithium reagents with chlorophosphines, and is intolerant to a wide variety of functional groups.[17] The second method is the transition metal-catalyzed phosphination. Both nickel- and palladium-catalyzed phosphination of

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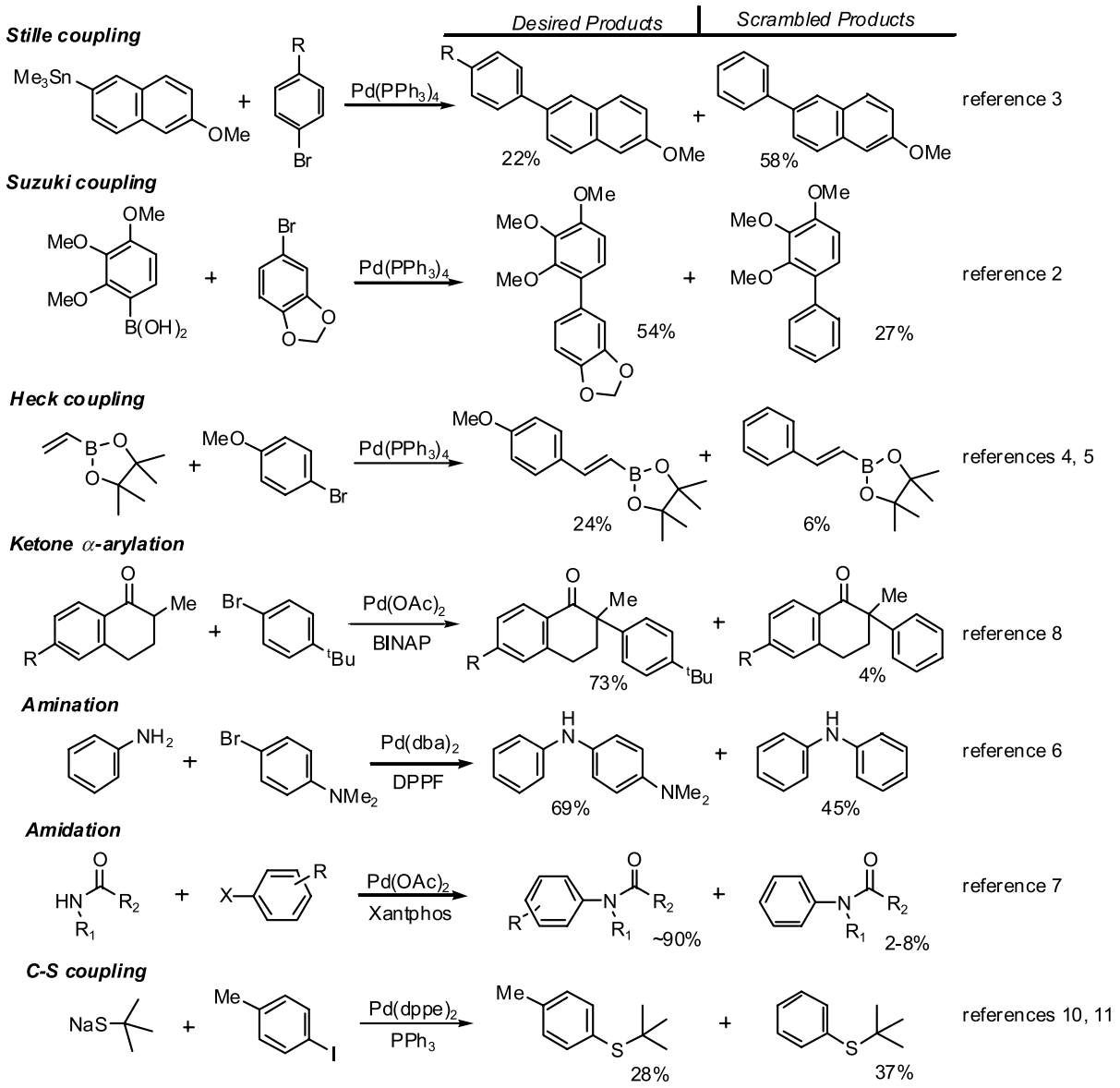


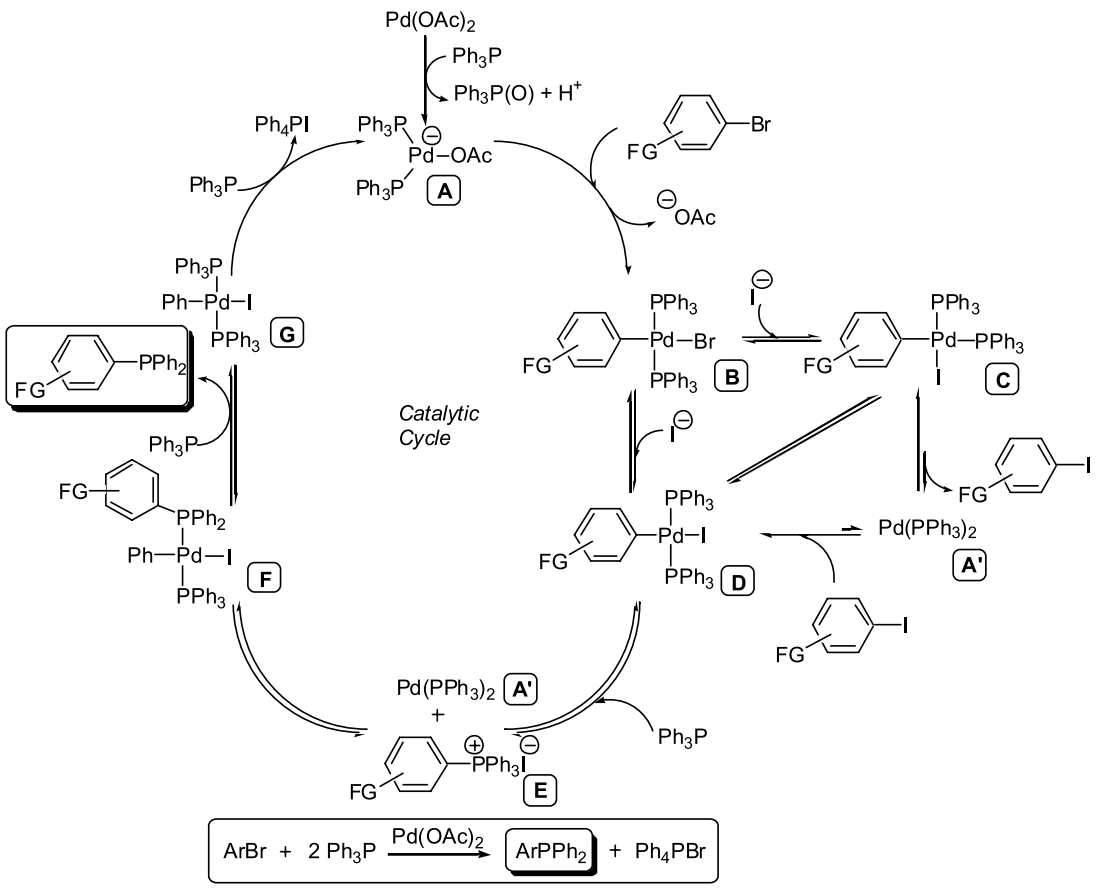
Scheme 1. Product scrambling in palladium-catalyzed cross-coupling reactions.

aryl triflates/halides using diphenylphosphine[18,19] (Ph_2PH) or chlorodiphenylphosphine[20] (Ph_2PCl) were reported recently.[21] The pioneering work of Stille using Pd/$TMSPPh_2$ system showed C–P bond formation from aryl iodides.[22] An alternative two-steps phosphine synthesis using Pd/$Ph_2P(O)H$ protocol requires subsequent reduction.[23] Recently, Lipshutz and co-workers have reported attractive C–P coupling method from aryl sulfonates using Pd/phosphine–borane system.[24] In the meanwhile, both Buchwald and Venkataraman groups disclosed an inexpensive copper-catalyzed phosphination of aryl iodides.[25] Herein, we report the palladium-catalyzed phosphination of functionalized aryl bromides using readily available triarylphosphines as the phosphinating agents to synthesize functionalized aryl phosphines.[26]

2. Results and discussion

Our initial discovery that pyridyl aryl triflates underwent successful catalyzed phosphination with triarylphosphines has prompted us to extend the method to aryl halides.[27] 4-Bromoacetophenone was therefore chosen as the prototypical substrate for screening the optimal reaction conditions. Both palladium(II) acetate and tetrakis(triphenylphosphine) palladium(0) complexes catalyzed the phosphination. A lower yield of the reaction was observed when $Pd_2(dba)_3$ complex was used, since dba (*trans*-dibenzylidieneacetone) ligand, has similar chromatographic behavior with the desired products and the purification procedure became more difficult. Therefore, palladium(II) acetate catalyst was preferred. The optimal amounts of triphenylphosphine added to the reaction were found to be 2.3–2.5 equiv. with respect to aryl bromide.[27] The optimized reaction conditions were then applied to the synthesis of other functionalized aryl phosphines (Table 1 and Eq. 3).

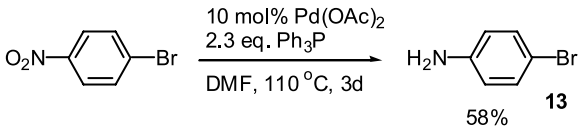
4-Bromobenzaldehyde was directly phosphinated by triphenylphosphine to form 4-(diphenylphosphino)benzaldehyde (Table 1, entry 1). In contrast, the previous preparation



Scheme 2. A plausible mechanism for palladium-catalyzed phosphination with added iodides.

of this phosphine, which finds many applications for water-soluble polymers[28] and porphyrins,[29] involved a muti-step synthesis requiring protection/deprotection of the aldehyde group.[30] Other functional groups, such as ester, nitrile, keto, ether and chloride are tolerant to this phosphination reaction (Table 1, entries 2–6). In contrast, previous syntheses of ester and nitrile containing phosphines required a long synthetic pathway.[31] Heterocyclic substrates, 3-bromopyridine and 2-bromothiophene were found to be compatible in this reaction (Table 1, entries 11–12).

Similar rates of reaction were observed for electronically different non-coordinating aryl bromides. The rate of the reaction of coordinating substrates, which contain ester, aldehyde, nitrile, pyridyl and thiophenyl groups required a longer reaction time (Table 1, entries 1, 3, 4, 11 and 12). Presumably strongly coordinating substrates rendered the catalyst complex coordinatively saturated and hence reduced the catalytic efficiency.



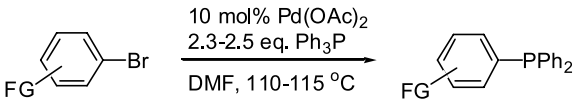
(4)

Some limitations of the substrates used in the palladium-catalyzed phosphination reaction exist. 4-Nitrobromobenzene was found to react quickly within 12 h at 110 °C to give no desired phosphinated-product but the 4-bromoaniline in 58% yield (Eq. 4). Reduction of the nitro-group was therefore very facile.[32] *ortho*-Substituted substrates such as 2-bromoanisole and 2-bromotoluene were found to be ineffective. These starting materials were recovered almost quantitatively after the reaction was heated for 72 h at 110 °C.

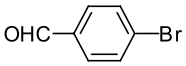
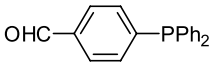
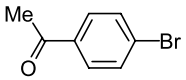
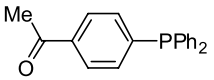
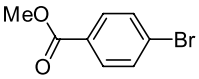
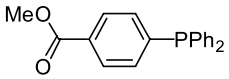
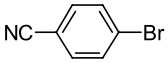
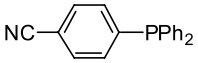
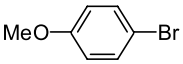
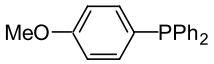
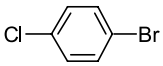
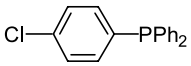
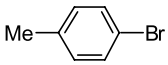
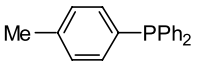
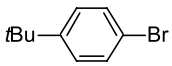
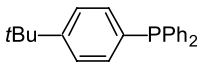
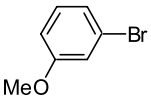
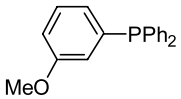
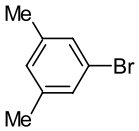
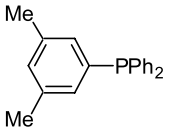
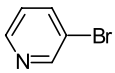
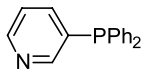
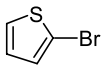
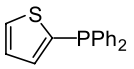
Other triarylphoshphines were found to be efficient diarylphosphinating agents for palladium catalyzed phosphination of aryl bromides (Table 2 and Eq. 5). The *p*-bromoacetophenone was diarylphosphinated by trixylylphosphine, tri(*p*-methoxyphenyl)phosphine and tri(*p*-tolyl)phosphine to yield the corresponding aromatic phosphines in moderate yields with similar rate (Table 2, entries 1–3). Sterically hindered tri(*o*-tolyl)phosphine did not react at all (Table 2, entry 4). These examples demonstrate the generality for diarylphosphination to synthesize various sterically unhindered aryl phosphines.

A user-friendly, economically attractive and environmentally benign phosphination was successfully carried out in solvent-free conditions (Table 3).[33] No significant electronic effect was observed in the solvent-free phosphination since both electron-withdrawing and donating substrates exhibited similar reaction rates (Table 3). *ortho*-Substituted aryl bromides still did not react in solvent-free conditions even at elevated temperature at 140 °C. The rates of the reactions in solvent-free conditions were slower than those in DMF. Presumably, the high viscosity of the reaction mixture was responsible. As Ph_3P melts at 79 °C, at the reaction temperature of 110 °C, triphenylphosphine behaved as the solvent, ligand and phosphinating agent.

Table 1. Palladium-catalyzed phosphination of aryl bromides with triphenylphosphine[a]



(3)

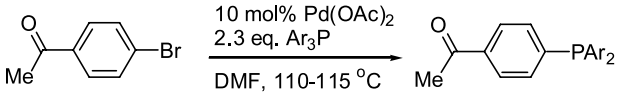
Entry	Substrate	Product	Time (h)	% Yield[b]
1		 **1**	64	32
2		 **2**	20	40
3		 **3**	36	30
4		 **4**	48	36
5		 **5**	24	27
6		 **6**	20	51[c]
7		 **7**	26	58[c]
8		 **8**	19	59[c]
9		 **9**	18	38
10		 **10**	18	51[c]
11		 **11**	72	25
12		 **12**	48	54[c]

[a] Reaction conditions: ArBr (1.0 mmol), Ph_3P (2.3–2.5 mmol), $Pd(OAc)_2$ (10 mol%) in DMF (4.0 mL) at 110–115 °C under nitrogen atmosphere.
[b] Isolated yield.
[c] GC yield in average of 2 runs.

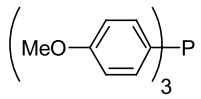
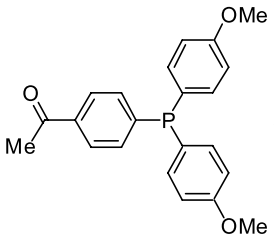
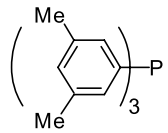
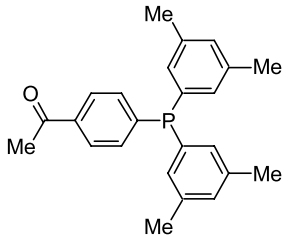
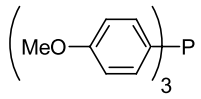
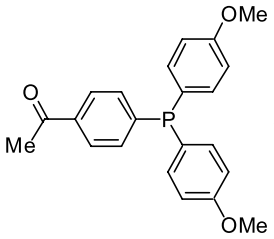
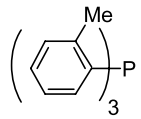
Halides have been discovered to be promoters in many transition metal-catalyzed processes and have become an important aspect of catalysis optimization.[34] To further optimize the phosphination, we had investigated the effect of halides and other anions in palladium-catalyzed phosphination of aryl bromides. Sodium iodide was used as the prototypical salt to examine the salt-effect in this reaction (Table 4). We found that the addition of 2.5 equiv. of NaI to the reaction mixture did enhance the yield. The optimal loading of NaI added was found to be around 5 equiv. (Table 4). A higher loading of 10 equiv. of NaI gave a lower yield of the product.

Other salts were also examined (Table 5). All halides gave

Table 2. Palladium-catalyzed phosphination of 4-bromoacetophenone with triarylphosphines[a]



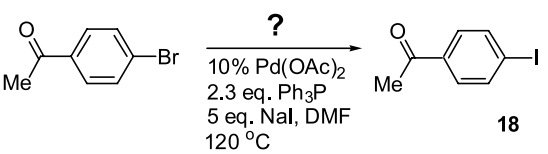
(5)

Entry	PAr_3	Product	Time (h)	% Yield[b]
1		 **14**	33	39
2		 **15**	32	34
3		 **16**	34	33
4			72	No rxn.[c]

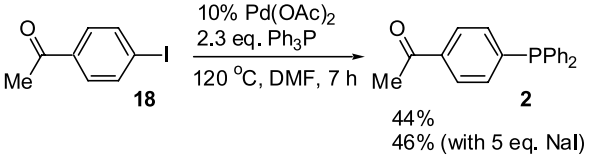
[a] Reaction conditions: 4-bromoacetophenone (1.0 mmol), Ar_3P (2.3 mmol), $Pd(OAc)_2$ (0.1 mmol, 10 mol%) in DMF (4.0 mL) at 110–115 °C under nitrogen atmosphere.
[b] Isolated yield.
[c] Starting material was recovered.

better yields or faster rate of the reaction (Table 5, entry 1 vs. 2–5, 8–10). Among the halides, sodium salts exhibited an equal or better promoting effect than potassium salts (Table 5, entries 3–5, 8–9). Iodide (MI, M=Li, Na, K, Et_4N) salts showed faster rate of reaction and higher yield of the product (Table 5, entries 2, 3, 8, 10). Alkali metal iodide generally gave higher yields of reaction compared with ammonium salts (Table 5, entries 1–2, 8 vs. 10). The best result was found to be with the addition of 5 equiv. of NaI, with the isolated yield of 4-(diphenylphosphino)acetophenone obtained in 60%. Non-halide salts such as, $NaBF_4$, $NaPF_6$ and NH_4PF_6 were found to be inferior (Table 5, entries 6, 7, 11).

The metal halides likely play several roles in the phosphination. Firstly, the addition of salts to the reaction increased the solvent polarity in the bulk environment, which favors the oxidative addition and formation of phosphonium salt intermediate (Scheme 2). Secondly, the iodide salt may assist the halide exchange for aryl bromide to aryl iodide,[35] and hence provide a lower energy barrier for oxidative addition of carbon–halogen bond with palladium catalyst. The possibility of converting aryl bromides into aryl iodides by the addition of NaI was supported by the observation of a trace amount of 4-iodoacetophenone generated during the course of the phosphination of 4-bromoacetophenone by GC–MS analysis (Eq. 7 and Scheme 2).



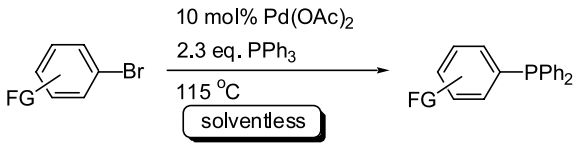
(7)

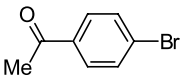
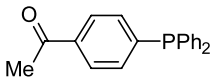
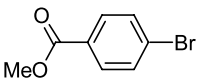
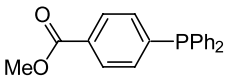
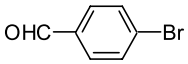
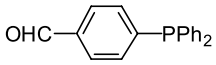
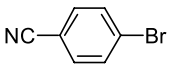
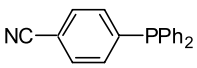
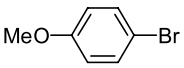
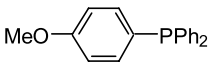
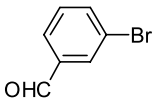
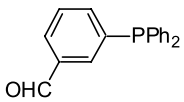
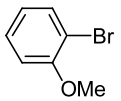
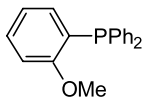
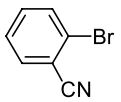
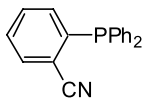


(8)

The more reactive 4-iodoacetophenone likely undergoes fast oxidative addition with palladium catalyst in the

Table 3. Solvent-free palladium-catalyzed phosphination of aryl bromides[a]

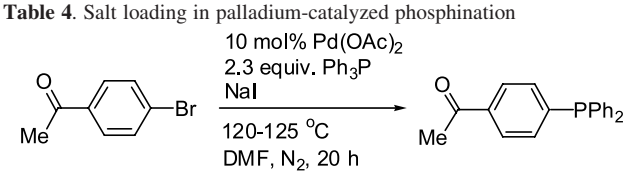


Entry	Substrate	Product	Time (h)	% Yield[b]
1		 **2**	1.5	44
2		 **3**	2.5	40
3		 **1**	2.5	40
4		 **4**	2.5	38
5		 **5**	1.0	33
6		 **17**	2.5	34
7			7	No rxn.[c]
8			7	No rxn.[c]

[a] Reaction conditions: ArBr (1.0 mmol), Ph_3P (2.3 mmol), and $Pd(OAc)_2$ (0.1 mmol, 10 mol%) at 110–115 °C under nitrogen atmosphere.
[b] Isolated yield.
[c] Reaction temperature (140 °C).

catalytic cycles (Scheme 2). Indeed, 4-iodoacetophenone reacted about three times faster than 4-bromoacetophenone (Eq. 8). Similar metal iodide acceleration phenomenon in the cross-coupling reactions have been observed.[36] Moreover, as iodide anion is less coordinating, therefore it dissociates more rapidly than bromides and chlorides,[34] and the concentration of coordinatively unsaturated palladium species would increase. Pd–aryl/P–aryl exchanges would be more facile as reported by Grushin on the addition step.[16] Hence a faster rate of reaction was observed (Table 5, entries 2, 3, 8, 10). The possibility of iodide anion in forming a new pentacoordinated anionic palladium species,[37] which facilitates the subsequent reductive elimination, could not be excluded.

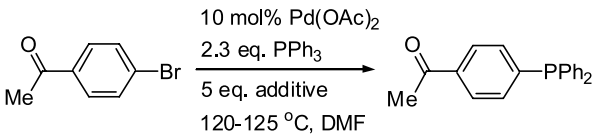
Table 4. Salt loading in palladium-catalyzed phosphination



Entry	NaI (equiv).	% GC yield
1	0	44
2	2.5	56
3	5	68
4	10	56

Scheme 2 illustrates a plausible mechanism for the reaction involving Pd(0)/Pd(II) cycles. Palladium(II) acetate is in situ reduced by triphenylphosphine to form acetate ligated complex **A**, $PdL_2(OAc)^-$ (L=triphenylphosphine).[38,39] This active anionic palladium complex **A** then undergoes oxidative addition with an aryl bromide to afford palladium complex **B** (Scheme 2).[40] Halide exchange by the addition of iodide ion (from NaI or KI) generated complexes **C** and **D**.[37] As we have observed that a trace amount of 4-iodoacetophenone formed during the course of the reaction by GC–MS analysis,[41] the ligand substitution

Table 5. Salt effects in palladium-catalyzed phosphination of aryl bromide[a]



(6)

Entry	Additive	Time (h)	% Yield[b]
1	/	20	40[c]
2	LiI	6	51
3	NaI	20	68 (60)[c]
4	NaBr	23	65
5	NaCl	23	51
6	$NaBF_4$	22	34
7	$NaPF_6$	20	0
8	KI	10	67
9	KBr	10	40
10	Et_4NI	2	49
11	NH_4PF_6	20	0

[a] Reaction conditions: ArBr (1.0 mmol), Ph_3P (2.3 mmol), additive (5.0 mmol) and $Pd(OAc)_2$ (0.1 mmol, 10 mol%) in DMF (4.0 mL) at 120–125 °C under nitrogen atmosphere.
[b] GC yield.
[c] Isolated yield.

product from **B** to **C** is feasible. A new equilibrium from **C**–**A′**–**D** would be established (Scheme 2). The *trans*-complex **D** subsequently undergoes iodide dissociation and reductive elimination with triphenylphosphine to produce a phosphonium salt **E** and palladium complex **A′**. Such Pd-catalyzed phosphonium salt formation for *meta*- and *para*- but not *ortho*-substituted aryl bromides has been reported.[42] Grushin *et al.* also reported that the iodide can facilitate the Pd–aryl/P–aryl interchange through the phosphonium salt pathway in the $ArPdX(PPh_3)_2$ complex.[43]

The anionic palladium complex **A** or **A′** undergoes oxidative addition by carbon–phosphorus bond activation of the phosphonium salt **E** to generate the coordinated $ArPPh_2$ Pd-complex (Scheme 2).[44,45] Finally, ligand substitution by triphenylphosphine to Pd(II) complex **F** gives $ArPPh_2$ and Pd–phenyl complex **G**. The PdL_2I^- species is regenerated by reductive elimination of triphenylphosphine and Pd bound phenyl group to yield the tetraphenylphosphonium iodide co-product (Scheme 2). The formation of tetraphenylphosphonium co-product was detected by ^{31}P NMR (δ=24.0 ppm)[46] in the reaction mixture. Therefore, two equivalents of PPh_3 were required. The first one serves as the diphenylphosphinating agent and the second one yields the phosphonium salt co-product.

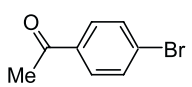
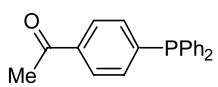
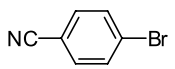
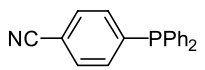
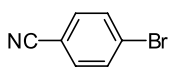
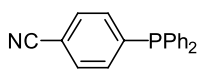
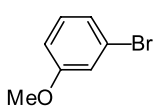
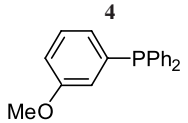
The iodide promoting effect in the phosphination was found to be general for aryl bromides and the results are listed in Table 6. Both the rates and about 10–20% increase in product yields were observed.

3. Conclusion

In conclusion, a catalytic user-friendly palladium-catalyzed phosphination using triarylphosphines as the phosphinating reagents was developed and optimized. This carbon–phosphorus bond formation was compatible with a number of functional groups, including aldehyde, keto, ester, nitrile, ether, pyridyl and thiothenyl group. This phosphination utilizes the air-stable triphenylphosphine as the phosphinating reagent and the reaction were carried out in neutral media. This process has a great potential to tailor a variety of substituted phosphines by using different triarylphopshines with various functionalized aryl bromides.

Table 6. Palladium-catalyzed phosphination of aryl bromides with iodide salts[a]

(9)

Entry	Substrate	Product	Salt	Time (h)	% Yield[b]
1		 **2**	KI	10	60
2		 **4**	NaI	48	52
3		 **4**	KI	16	49
4		 **9**	KI	12	42

[a] Reaction conditions: ArBr (1.0 mmol), Ph_3P (2.3 mmol), $Pd(OAc)_2$ (0.1 mmol, 10 mol%) and salt (5.0 mmol) in DMF (4.0 mL) under nitrogen atmosphere at 120–125 °C
[b] Isolated yield.

4. Experimental

4.1. General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. Hexane for chromatography was distilled from anhydrous calcium chloride. *N*,*N*-Dimethylformamide was distilled from magnesium sulfate under reduced pressure.[47] Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck, 70–230 and 230–400 mesh) was used for column chromatography. ^{1}H NMR spectra were recorded on a Brüker DPX 300 (300 MHz) spectrometer. Spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm), or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Brüker DPX 300 (75 MHz) spectrometer and referenced to $CDCl_3$ (δ 77.00 ppm). ^{31}P NMR spectra were recorded on a Varian 400 (162 MHz) and referenced to 85% H_3PO_4 externally. Coupling constants (J) were reported in Hertz (Hz). Mass spectra (EIMS and FABMS) were recorded on a HP 5989B Mass Spectrometer. High resolution mass spectra (HRMS) were obtained on a Brüker APEX 47e FT-ICR mass spectrometer (ESIMS). GC–MS analysis was conducted on a HP G1800C GCD system using a HP5MS column (30 m×0.25 mm). The products described in GC yield according to the authentic samples/anthracene calibration curve.

General procedure A: palladium-catalyzed phosphination of aryl bromides in DMF. Aryl bromides (1.0 mmol), triphenylphosphine (655 mg, 2.5 mmol) and $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%) were charged to a Teflon screw-capped Schlenk flask. Evacuated and backfilled with nitrogen three times. The Schenk flask was then added dry DMF (4.0 mL) under nitrogen. The solution was heated to 110–115 °C for a specified time in Table 1 and generally the color of the solution changed from yellow to red. The reaction was cooled down and DMF was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain the pure product.

General procedure B: palladium-catalyzed phosphination of aryl bromides under solventless conditions. Aryl bromides (1.0 mmol), triphenylphosphine (603 mg, 2.3 mmol) and $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%) were charged to a Teflon screw-capped Schlenk flask. Evacuated and backfilled with nitrogen three cycles. The solution was heated to 115 °C for a specified time in Table 3. The reaction was cooled down and dichloromethane was added. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain the pure product.

General procedure C: palladium-catalyzed phosphination of aryl bromides in the presence of salts. Aryl bromides (1.0 mmol), triphenylphosphine (603 mg, 2.3 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 10 mol%) and salt (5.0 mmol) were charged to a Teflon screw-capped Schlenk flask. Evacuated and backfilled with nitrogen three times. The Schenk flask was then added dry DMF (4.0 mL) under nitrogen. The solution was heated to 120–125 °C for a specified time in Tables 4 and 5. The reaction was cooled down and DMF was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate to obtain the pure product.

4.1.1. 4-(Diphenylphosphino)benzaldehyde (1).[48] General procedure A was followed. R_f=0.6 (hexane/ethyl acetate=10:1). Mp 75.5–77 °C (lit. 69–71 °C).[49] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.43 (m, 12H), 7.80 (dd, 2H, J=8.1, 1.5 Hz), 10.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.8 (d, J_{CP}=7.2 Hz), 129.3, 133.5 (d, J_{CP}=18.3 Hz), 134.0 (d, J_{CP}=20.0 Hz), 135.7 (d, J_{CP}=10.4 Hz), 136.0, 146.5 (d, J_{CP}=15.5 Hz), 191.9; ^{31}P (162 MHz, $CDCl_3$) δ −3.41; MS (EI): *m*/*z* (relative intensity) 290 (M^+, 100), 261 (8), 211 (9), 183 (95), 165 (12), 152 (20).

4.1.2. 4-(Diphenylphosphino)acetophenone (2).[50] General procedure A was followed. R_f=0.2 (hexane/ethyl acetate=20:1). Mp 118–120 °C (lit. 119–120 °C).[50] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 7.29–7.38 (m, 12H), 7.88 (dd, 2H, J=8.3, 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 127.9 (d, J_{CP}=6.2 Hz), 128.6 (d, J_{CP}=7.2 Hz), 129.1, 133.2 (d, J_{CP}=18.5 Hz), 133.9 (d, J_{CP}=19.9 Hz), 135.9 (d, J_{CP}=10.4 Hz), 136.7, 144.3 (d, J_{CP}=14.2 Hz), 197.8; MS (EI): *m*/*z* (relative intensity) 304 (M^+, 100), 289 (10), 261 (12), 227 (11), 183 (90), 152 (30).

4.1.3. Methyl 4-(diphenylphosphino)benzoate (3).[51] General procedure A was followed. R_f=0.6 (hexane/ethyl acetate=10:1). Mp 103–105 °C (lit. 99–100 °C).[49] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.38 (m, 12H), 7.97 (dd, 2H, J=8.4, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 128.7 (d, J_{CP}=7.1 Hz), 129.1, 129.3 (d, J_{CP}=6.4 Hz), 133.0, 133.1 (d, J_{CP}=18.5), 133.9 (d, J_{CP}=19.9 Hz), 136.1 (d, J_{CP}=10.5 Hz), 144.0 (d, J_{CP}=14.0 Hz), 166.9; MS (EI): *m*/*z* (relative intensity) 320 (M^+, 100), 289 (8), 261 (7), 207 (9), 183 (70), 166 (12).

4.1.4. 4-(Diphenylphosphino)benzonitrile (4).[52] General procedure A was followed. R_f=0.6 (hexane/ethyl acetate = 10:1). Mp 86–87 °C (lit. 86–87 °C).[49] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.39 (m, 12H), 7.57 (dd, 2H, J=8.4, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.8, 118.9, 128.8 (d, J_{CP}=7.4 Hz), 129.5, 131.7 (d, J_{CP}=5.9 Hz), 133.4 (d, J_{CP}=18.4 Hz), 134.0 (d, J_{CP}=20.2 Hz), 135.3 (d, J_{CP}=10.3 Hz), 145.1 (d, J_{CP}=16.5 Hz); MS (EI): *m*/*z* (relative intensity) 287 (M^+, 100), 208 (55), 195 (8), 183 (62), 177 (12).

4.1.5. 4-(Diphenylphosphino)anisole (5).[53] General procedure A was followed. Mp 64.5–65.5 °C (lit. 63–65 °C).[50b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 7.10 (dd, 2H, J=8.1, 4.0 Hz), 7.24–7.59 (m, 12H); MS (EI): *m*/*z* (relative intensity) 292 (M^+, 100), 277 (12), 259 (10), 215 (30), 183 (48).

4.1.6. 3-(Diphenylphosphino)anisole (9).[54] General procedure A was followed. R_f=0.4 (hexane/ethyl acetate = 20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H),

6.83–6.90 (m, 3H), 7.22–7.34 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.1, 114.3, 118.9 (d, J_{CP}=21.1 Hz), 126.0 (d, J_{CP}=18.8 Hz), 128.5 (d, J_{CP}=6.8 Hz), 128.7, 129.5 (d, J_{CP}=7.7 Hz), 133.7 (d, J_{CP}=19.4 Hz), 137.0 (d, J_{CP}=10.6 Hz), 138.7 (d, J_{CP}=11.0 Hz), 159.5 (d, J_{CP}=8.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ −3.81; MS (EI): *m/z* (relative intensity) 292 (M^+, 100), 213 (22), 199 (20), 183 (48).

4.1.7. 3-(Diphenylphosphino)pyridine (11).[55] General procedure A was followed. R_f=0.8 (hexane/ethyl acetate=5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, 1H, *J*=1.4 Hz), 8.30 (d, 1H, *J*=8.3 Hz), 7.92 (t, 1H, *J*=8.2 Hz), 7.27–7.69 (m, 11H); MS (EI): *m/z* (relative intensity) 263 (M^+, 100), 186 (20).

4.1.8. 4-(Di(4-tolyl)phosphino)acetophenone (14). General procedure A was followed. 4-Bromoacetophenone (199 mg, 1.0 mmol), palladium(II) acetate (22.4 mg, 0.1 mmol), tri(4-tolyl)phosphine (699 mg, 2.3 mmol) and dry DMF (4 mL) were used to obtain 4-(di(4-tolyl)phosphino)acetophenone (**14**) (129 mg, 39%) as light yellow solid after purified by column chromatography on silica gel using a solvent mixture (hexane/ethyl acetate=10:1) as the eluent. R_f=0.4 (hexane/ethyl acetate=10:1). Mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 6H), 2.57 (s, 3H), 7.15–7.25 (m, 8H), 7.36 (dd, 2H, *J*=8.4, 1.5 Hz), 7.86 (dd, 2H, *J*=8.4, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 26.6, 127.9 (d, J_{CP}=6.0 Hz), 129.5 (d, J_{CP}=7.5 Hz), 132.7 (d, J_{CP}=9.0 Hz), 133.0 (d, J_{CP}=18.2 Hz), 134.0 (d, J_{CP}=20.3 Hz), 136.5, 139.2, 145.3 (d, J_{CP}=14.3 Hz), 197.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.60; MS (EI): *m/z* (relative intensity) 332 (M^+, 100), 317 (5), 289 (10), 281 (7), 241 (8), 211 (30), 197 (28); HRMS (ESIMS) calcd for $C_{22}H_{21}OPH^+$ 333.1408, found 333.1385.

4.1.9. 4-(Bis(3,5-dimethylphenyl)phosphino)acetophenone (15). General procedure A was followed. 4-Bromoacetophenone (199 mg, 1.0 mmol), palladium(II) acetate (22.4 mg, 0.1 mmol), trixylylphosphine (796 mg, 2.3 mmol) and dry DMF (4 mL) were used to yield 4-(bis(3,5-dimethyl)phosphino)acetophenone (**15**) (122 mg, 34%) as pale yellow solid after purified by column chromatography on silica gel using a solvent mixture (hexane/ethyl acetate=10:1) as the eluent. R_f=0.6 (hexane/ethyl acetate = 10:1). Mp 56–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 12H), 2.59 (s, 3H), 6.93 (s, 2H), 6.96 (s, 2H), 7.00 (s, 2H), 7.34 (dd, 2H, *J*=8.3, 1.4 Hz), 7.87 (dd, 2H, *J*=8.3, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 26.6, 127.9 (d, J_{CP}=6.2 Hz), 131.0, 131.7 (d, J_{CP}=20.2 Hz), 133.2 (d, J_{CP}=18.2 Hz), 135.7 (d, J_{CP}=9.5 Hz), 136.5, 138.1 (d, J_{CP}=7.9 Hz), 145.1 (d, J_{CP}=14.8 Hz), 198.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.88; MS (EI): *m/z* (relative intensity) 360 (M^+, 100), 345 (8), 317 (12), 253 (8), 241 (15), 225 (13), 211 (22), 193 (16); HRMS (ESIMS) calcd for $C_{24}H_{25}OPH^+$ 361.1721, found 361.1709.

4.1.10. 4-(Di(4-methoxyphenyl)phosphino)acetophenone (16). General procedure A was followed. 4-Bromoacetophenone (199 mg, 1.0 mmol), palladium(II) acetate (22.4 mg, 0.1 mmol), tri(4-methoxyphenyl)phosphine (810 mg, 2.3 mmol) and dry DMF (4 mL) were used to yield 4-(di(4-methoxyphenyl)phosphino)acetophenone (**16**) (120 mg, 33%) as pale yellow solid after purified by column chromatography on silica gel using a solvent mixture (hexane/ethyl acetate=10:1) as the eluent. R_f=0.2 (hexane/ethyl acetate=10:1). Mp 54–56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.81 (s, 6H), 6.90 (dd, 4H, *J*=6.0, 2.1 Hz), 7.25–7.32 (m, 6H), 7.85 (dd, 2H, *J*=8.4, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 55.2, 114.3 (d, J_{CP}=8.3 Hz), 127.1 (d, J_{CP}=7.4 Hz), 127.8 (d, J_{CP}=5.8 Hz), 132.6 (d, J_{CP}=17.7 Hz), 135.5 (d, J_{CP}=21.5 Hz), 136.3, 146.1 (d, J_{CP}=13.9 Hz), 160.5, 197.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ −13.03; MS (EI): *m/z* (relative intensity) 364 (M^+, 100), 349 (10), 281 (9), 257 (10), 245 (30), 229 (8), 214 (40), 199 (18); HRMS (ESIMS) calcd for $C_{22}H_{21}O_3PH^+$ 365.1307, found 365.1289.

4.1.11. 3-(Diphenylphosphino)benzaldehyde (17).[56] General procedure B was followed. R_f=0.6 (hexane/ethyl acetate=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.43 (m, 12H), 7.80 (dd, 2H, *J*=8.1, 1.5 Hz), 10.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.8 (d, J_{CP}=7.2 Hz), 129.3, 133.5 (d, J_{CP}=18.3 Hz), 134.0 (d, J_{CP}=20.0 Hz), 135.7 (d, J_{CP}=10.4 Hz), 136.0, 146.5 (d, J_{CP}=15.5 Hz), 191.9; ^{31}P (162 MHz, $CDCl_3$) δ −3.41; MS (EI): *m/z* (relative intensity) 290 (M^+, 100), 261 (8), 211 (9), 183 (95), 165 (12), 152 (20).

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