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A new synthesis of 3,5-dihydroxy-7-(1-pyrrolyl)-6-heptenoic acids, a family of HMGCoA reductase inhibitors with antifungal activity

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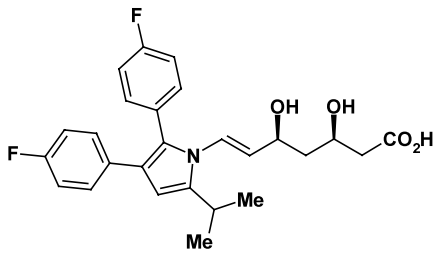
Abstract—Starting from a 3,5-dihydroxyheptanoic acid derivative, a new synthesis of pyrrole statins that contain a double bond on the dihydroxyacid chain has been developed. Key steps are *N*-acylamino acid enamide formation through enamine trapping with aromatic acyl chlorides and subsequent münchnone cycloaddition with activated acetylenes.

In the course of our search for new antifungal agents we have found that pyrrole containing statins such as **1** inhibit fungal growth. Statins, compounds bearing the 3,5-dihydroxyheptenoic structural motif, are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and are widely used as cholesterol-lowering agents in clinical practice.[1] The antifungal activity might be explained taking into account that part of the mevalonate biosynthetic pathway, including HMGR, is common to both fungi and mammals. Antifungal activity has also been reported for Fluvastatin, a totally synthetic statin bearing an indole moiety, and not for those coming from natural sources that bear modified decalines.[2] Preliminary SAR showed that the unsaturation in the dihydroxyacid chain was important for the antifungal activity. The reported synthesis for **1** starts from the synthesis of the pyrrole moiety and then the dihydroxyacid chain is built following a multistep sequence.[3] This synthetic strategy implies that the dihydroxyheptenoic acid side chain which is common to all compounds have to be constructed for every derivative. At this point, a new synthetic route which incorporates the 3,5-dihydroxy-6-heptenoic acid moiety into the common precursor used as starting material and allows for a flexible and easy substitution at all the pyrrole ring positions was desirable. A synthesis has been published for the saturated chain version of **1** where the heterocycle is built on a precursor of the dihydroxyacid moiety.[4] In this case, a münchnone cycloaddition was performed with *N*-acyl-*N*-alkylamino acids and suitable acetylenes to build the heterocycle (Fig. 1) and, after that, the dihydroxyacid chain was synthesised in a similar manner as the above case.



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Results and discussion

The optimal synthetic sequence for our exploration should start from an advanced intermediate that contains the common dihydroxyacid fragment and allow us to vary in a systematic way the substitution of the

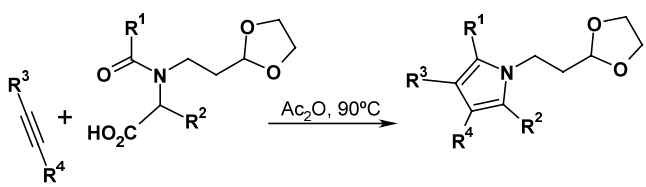

Figure 1.

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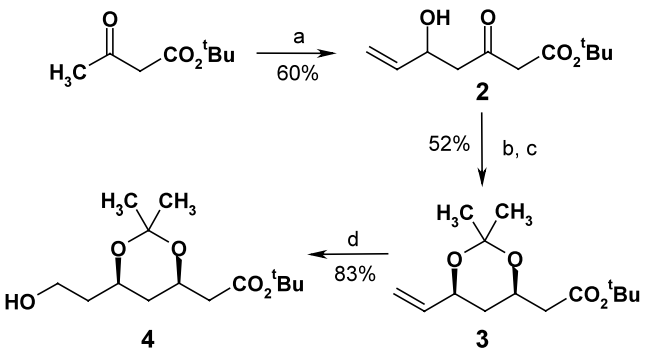
pyrrole heterocycle. To achieve this, münchnone cycloaddition seems to be a good strategy to build the heterocycle. However, conjugation of the side chain double bond with the cyclic azomethine–ylide dipole may modify the electronic content of the dipole and hence may also influence the reactivity towards the cycloaddition considered. Moreover, a synthetic sequence to prepare the *N*-acylamino acid precursor containing the unsaturated dihydroxyacid side chain has to be developed.

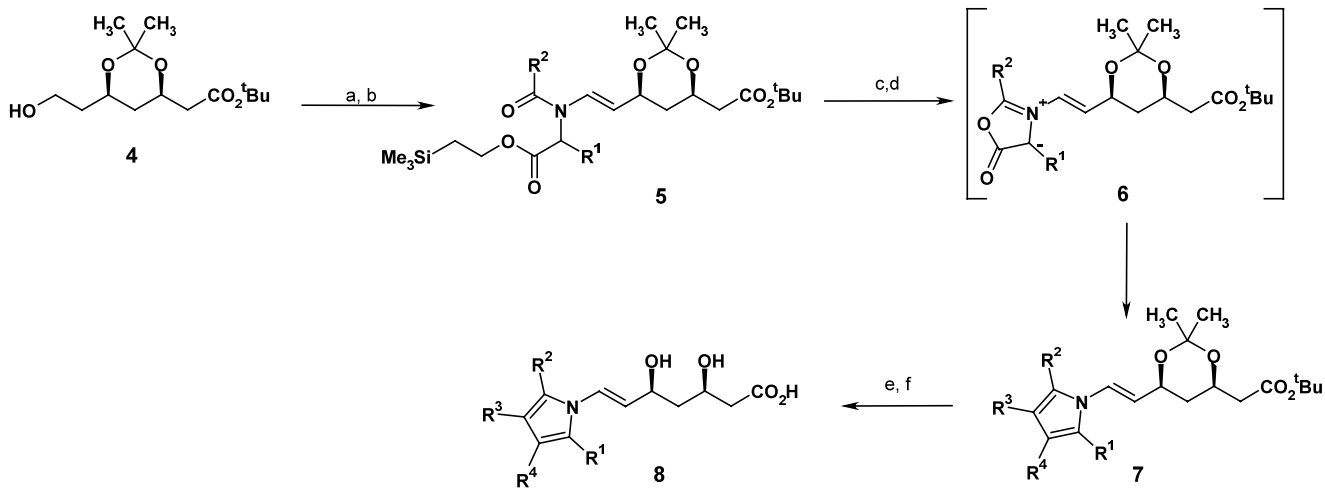
The common intermediate chosen was the protected alcohol **4**. It was prepared as a racemic mixture using slightly modified reported procedures to yield the desired *tert*-butyl ester[5] (Scheme 1). The *iso*-propylidene acetal was very useful for removing traces of the hydroxy epimer produced in the stereoselective reduction of the hydroxyketone **2**. Furthermore, this synthesis is amenable to enantiomer separation procedures based on chiral acetals, e.g. through menthonide derivatives.[6]



Scheme 1. *Reagents and conditions*: (a) i. THF, NaH, −20°C, ii. BuLi, −50°C, iii. Acrolein, −50 to −10°C; (b) Et_3B, THF/MeOH, −78°C, 1 h, then $NaBH_4$; (c) $(CH_3O)_2C(CH_3)_2$, TsOH; (d) i. 9-BBN, THF, −20°C to rt, then NaOH, rt, overnight.

The outcome of this strategy is shown in Scheme 2. Alcohol **4** was converted to aldehyde by Swern oxidation. The following step was the imine formation and the subsequent enamine trapping to yield the enamide **5**. The imine was smoothly formed using magnesium sulphate as dehydrating agent. Every amino acid we used (see R^1 in Table 1) reacted properly to afford the corresponding imine. After isolation, the imine was subjected to acylation with acyl chlorides and triethylamine as base.[7] This method was far more efficient than the use of carboxylic acids and condensating agents. Though different synthetic methods were tried for the acylation, we only obtained the desired *N*-acylenamines when aromatic carboxy derivatives were used.[8] Yields were good and did not seem to depend on the amino acid. The protecting group chosen for the amino acid carboxy group was 2-(trimethylsilyl)ethyl ester. This group is removed under essentially neutral conditions and the integrity of the sensitive enamide is preserved that way.

The key step was the 1,3-dipolar cycloaddition on the münchnone **6** obtained from *N*-acylamino acid enamine **5**. To our knowledge there is no report of a cycloaddition carried out on a münchnone which bears a conjugated double bond such as the one derived from **5**. A number of acetylenes bearing electron withdrawing groups were selected to carry out the cycloaddition (Table 1). This reaction proceeded well using acetic anhydride as an activating agent to form the cyclic dipole.[9] This was the way that cycloaddition was achieved for most of the acetylenes bearing ester, amide, ketone, sulphone or *p*-nitrophenyl as activating groups. Yields obtained were moderate to good and they have a rough correlation with the electron withdrawing efficiency of acetylene substituents. In this sense, yields for esters of acetylenedicarboxylic acid tend to be the best (entries a, l, m, o, r, x) and, on the other hand, yield for the *p*-nitrophenylacetylene was only modest (entry h).



Scheme 2. *Reagents and conditions*: (a) ClCOCOCl, DMSO, CH_2Cl_2, −78°C, then Et_3N; (b) $H_2NR^1CHCO_2CH_2CH_2Si(CH_3)_3$, $MgSO_4$, CH_2Cl_2; then R_2COCl, Et_3N; (c) Bu_4NF, THF; (d) R_3CCR_4, Ac_2O, toluene, 60°C; (e) 1N NaOH, THF.

Table 1. Yields and isomer ratios for enamides **3** and pyrrole cycloadducts **7**

Entry	R^1	R^2	**5** yield (%)	Major regioisomer		**7** combined yield (%)	Isomer ratio[a]
				R^3	R^4		
a	$(CH_3)_2CH$-	4-FC_6H_4-	70	CH_3OCO-	CH_3OCO-	66	–
b	$(CH_3)_2CH$-	4-FC_6H_4-	70	CH_3CH_2OCO-	H-	48	85:15
c	$(CH_3)_2CH$-	4-FC_6H_4-	70	$PhCH_2OCO$-	H-	47	>95:5
d	$(CH_3)_2CH$-	4-FC_6H_4-	70	$CH_3O(CH_2)_3OCO$-	H-	42	90:10
e	$(CH_3)_2CH$-	4-FC_6H_4-	70	CH_3CO-	H-	41	80:20
f	$(CH_3)_2CH$-	4-FC_6H_4-	70	PhCO-	H-	73	>95:5
g	$(CH_3)_2CH$-	4-FC_6H_4-	70	4-$CH_3C_6H_4SO_2$-	H-	56	75:25
h	$(CH_3)_2CH$-	4-FC_6H_4-	70	4-$NO_2C_6H_4$-	H-	15	65:35[b]
i	$(CH_3)_2CH$-	4-FC_6H_4-	70	H-	$(CH_3)_3CH_2CH_2NHCO$-	32	>95:5
j	$(CH_3)_2CH$-	4-FC_6H_4-	70	H-	$PhCH_2NHCO$-	50	60:40
k	$(CH_3)_2CH$-	4-FC_6H_4-	70	H-	4-FC_6H_4NHCO-	34	80:20
l	$(CH_3)_2CH_2CH_2$-	4-FC_6H_4-	74	CH_3OCO-	CH_3OCO-	65	–
m	CH_3OCH_2-	4-FC_6H_4-	62	CH_3OCO-	CH_3OCO-	54	–
n	CH_3OCH_2-	4-FC_6H_4-	62	4-$CH_3C_6H_4SO_2$-	H-	48	75:25
o	$CH_3SCH_2CH_2$-	4-FC_6H_4-	52	CH_3OCO-	CH_3OCO-	53	–
p	$CH_3SCH_2CH_2$-	4-FC_6H_4-	52	CH_3CH_2OCO-	H-	47	75:25
q	$CH_3SO_2CH_2CH_2$-	4-FC_6H_4-	75	H-	$PhCH_2NHCO$-	44	85:15
r	$PhCH_2$-	Ph-	71	CH_3OCO-	CH_3OCO-	82	–
s	$PhCH_2$-	Ph-	71	CH_3CH_2OCO-	H-	64	75:25
u	$PhCH_2$-	Ph-	71	CH_3CO-	H-	82	65:35
v	$PhCH_2$-	Ph-	71	4-$CH_3C_6H_4SO_2$-	H-	87	80:20
x	$PhCH_2$-	3,4,5-$CH_3OC_6H_2$-	59	CH_3OCO-	CH_3OCO-	63	–
y	$PhCH_2$-	3,4,5-$CH_3OC_6H_2$-	59	CH_3CH_2OCO-	H-	38	>95:5
z	$PhCH_2$-	3,4,5-$CH_3OC_6H_2$-	59	CH_3CO-	H-	65	70:30
aa	$PhCH_2$-	3,4,5-$CH_3OC_6H_2$-	59	4-$CH_3C_6H_4SO_2$-	H-	17	>95:5
ab	Ph-	Ph-	44	CH_3OCO-	CH_3OCO-	69	–
ac	Ph-	Ph-	44	CH_3CH_2OCO-	H-	63	–
ad	Ph-	Ph-	44	CH_3CO-	H-	77	–

[a] Ratio refers to isolated regioisomers unless otherwise stated.
[b] Isomer ratio determined by ^1H NMR.

The reaction always showed some degree of regioselection, giving isomer ratios ranging from a poor 6:4 regioselectivity (entry j) to the obtention of only one compound (entries c, f, i, y, aa). Regiochemistry of the cycloaddition was elucidated by ^1H NMR, making use of the chemical shifts of the benzyl-like hydrogens placed at C-2 or C-5 of the pyrrole nucleus in compounds **7**.[10] The general rule for our case is that the major regioisomer has the substituent coming from the acetylene dipolarophile *vicinal* to the aryl group R^2, as described in the literature.[11] Propiolic acid-derived amides are an exception to this rule. When this grouping is used as activating an electron withdrawing group for the cycloaddition, the major regioisomer has the amide group *vicinal* to the group coming from the aminoacid sidechain R^1 (entries i, j, k, q). To our knowledge, it is the first time this reverse regioselectivity has been reported. A reverse regioselection has been described for phenylacetylene and has been explained on the basis that it is an electron-rich dipolarophile.[11] This might be the case for propiolic acid-derived amides where the alkyne electron content is higher than in the ester case.

This change in regiochemistry opens synthetic possibilities for the regioselective obtention of carboxypyrrole derivatives by simply selecting an adequate ester or amide acetylene derivative to control the final substitution pattern.

In conclusion, a new synthetic entry to double bond containing statins has been developed. The extended conjugation of azomethine–ylide dipoles of structure **6** does not seem to significantly affect the 1,3-dipolar cycloaddition reaction. Finally, and for the case of carboxypyrrole derivatives, an efficient way of modulating the regiochemistry has been found by the appropriate selection of the propiolate derived dipolarophiles. Biological data on fungal growth inhibition for compounds described here will be reported elsewhere.

Acknowledgements

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7. *Experimental procedure*: The protected amino acid (16 mmol) and $MgSO_4$ (40 mmol) in CH_2Cl_2 (70 ml) were stirred at room temperature for 30 min; then, the aldehyde (16 mmol) in CH_2Cl_2 (40 ml) was slowly added over a period of 30 min and the resulting reaction mixture was stirred at rt for 3–5 h. The reaction was filtered and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 ml) containing dry Et_3N (50 mmol), cooled down to 0°C and a solution of the acid chloride (48 mmol) in CH_2Cl_2 (50 ml) was added over 30 min. The reaction was warmed up to rt and stirred for 15 h. Excess acid chloride was quenched with butylamine (40 mmol), solvents were evaporated and the residue was dissolved in EtOAc (200 ml), washed (satd $NaHCO_3$, 3×100 ml and brine 2×100 ml), dried (Na_2SO_4) and concentrated to dryness. Enamides **5** were purified by flash chromatography.
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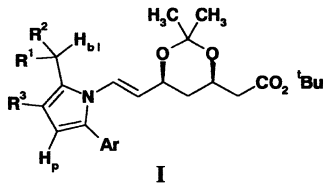
9. *Experimental procedure*: Enamide (1 mmol) was dissolved in 10% Ac_2O in toluene (10 ml), the alkyne (2 mmol) was added and the reaction mixture was stirred for 2 h at 60°C. The reaction was concentrated to dryness, the residue dissolved in EtOAc (100 ml), washed (H_2O, 2×50 ml and brine, 2×50 ml), dried (Na_2SO_4) and concentrated to dryness. Pyrroles **7** were purified by flash chromatography.
10. Pyrrole hydrogen (H_p) in compounds of structure **II** did not show splitting due to J_4 coupling with aliphatic hydrogens, as reported for analogous structures. However, chemical shifts for the benzyl-like hydrogens (H_{bl}) in regioisomers of structure **I**, where R^3 is always an electron withdrawing group, are consistently higher than chemical shifts for those present on compounds of structure **II**, this being an unambiguous way to assign adducts regiochemistry. (a) Coppola, B. P.; Noe, M. C.; Schartz, D. J.; Abdon, R. L., II; Trost, B. M. *Tetrahedron* **1994**, *50*, 93; (b) Dalla Croce, P.; Gariboldi, P.; La Rosa, C. *J. Heterocycl. Chem.* **1987**, *24*, 1793.



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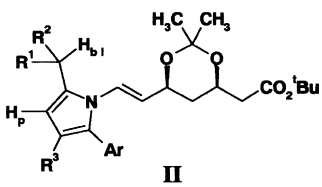

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