Ugi reactions of tertiary carboxylic acids: Combinatorial synthesis of glycyrrhetinic acid derivatives

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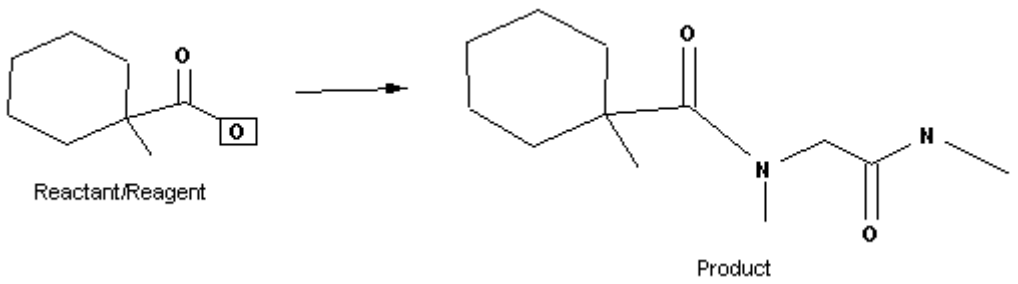
Abstract

A combinatorial library of alpha ketoamines was generated by the Ugi four component reaction on tertiary carboxylic acid

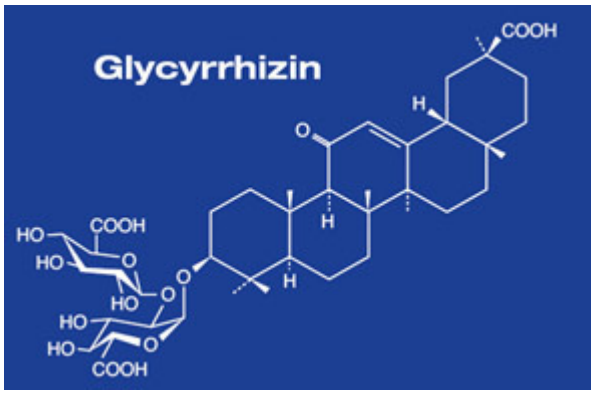
Introduction

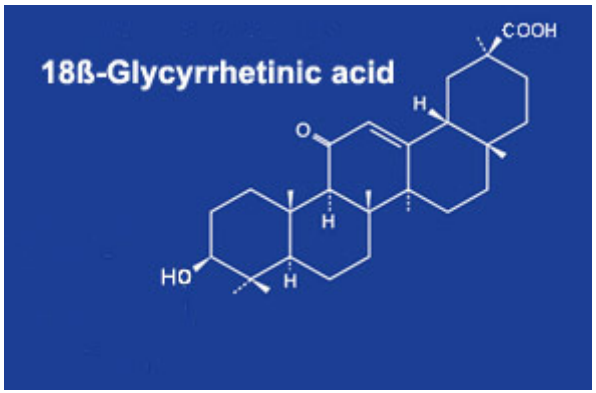
The dried rhizome and root of Glycyrrhiza glabra (also known as licorine or liquorice) were employed medicinally by the Egyptian, Chinese and Roman civilizations as an expectorant. The compound Glycyrrhizin from liqorice extracts has been used for more than 60 years in Japan to treat hepatitis and infection of Herpes simplex. Glycyrrhizin and its aglycone (18ß-glycyrrhetinic acid, GHA) inhibit growth and cytopatology of numerous RNA and DNA viruses, including hepatitis A [1] and C [2], human immunodeficiency virus HIV [3] and cytomegalovirus (CMV) [4]. 18alpha-glycyrrhetinic acid showed inhibitory activity in cell-free HIV infection systems [7].
Ugi reactions using tertiary carboxylic acids are still rare: e.g. only 9 references were found in SciFinder for the following reaction substructure:

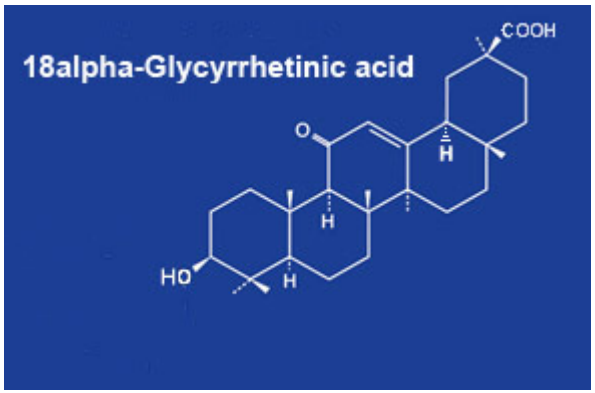
liquorice rods from glycyrrhiza glabra



Based on the findings of our earlier work of novel glycosilated analogs of glycyrrhetinic acid [5] we report here the use of glycyrrhizin and glycyrrhetinic acid as components in the Ugi reaction.

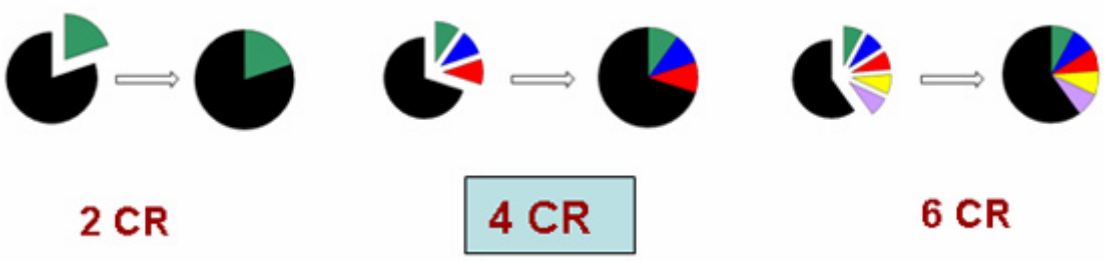






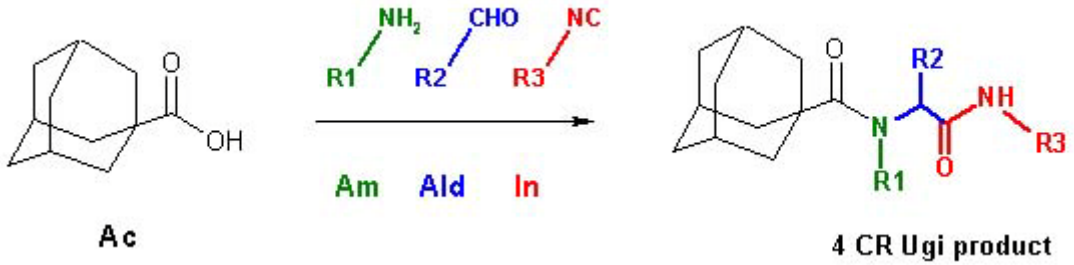
Multicomponent reactions (MCRs)

Multicomponent reactions are suitable for the synthesis of libraries of diverse small molecules. The four component Ugi condensation (Ugi 4 CR) between an aldehyde, amine, isonitrile and carboxylic acid is a powerful tool for rapid preparation of lead compounds in drug discovery.



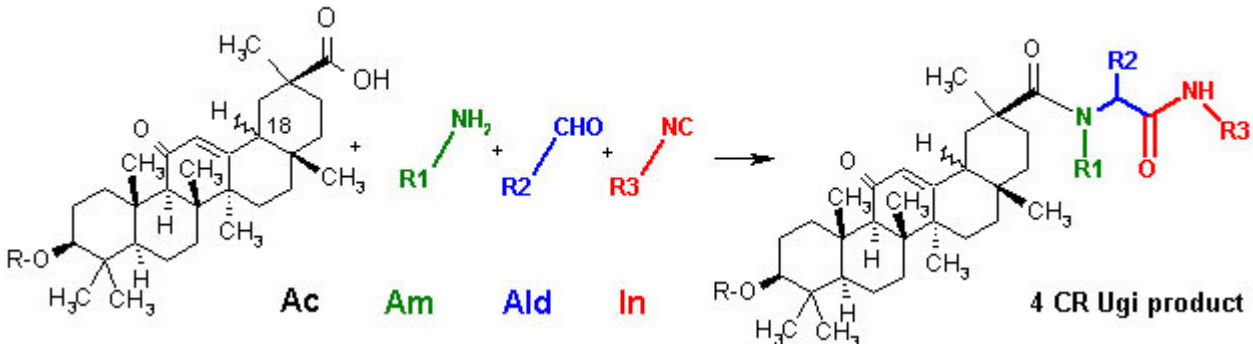
Results and discussion

As the model reaction employing adamantane carboxylic acid was successful



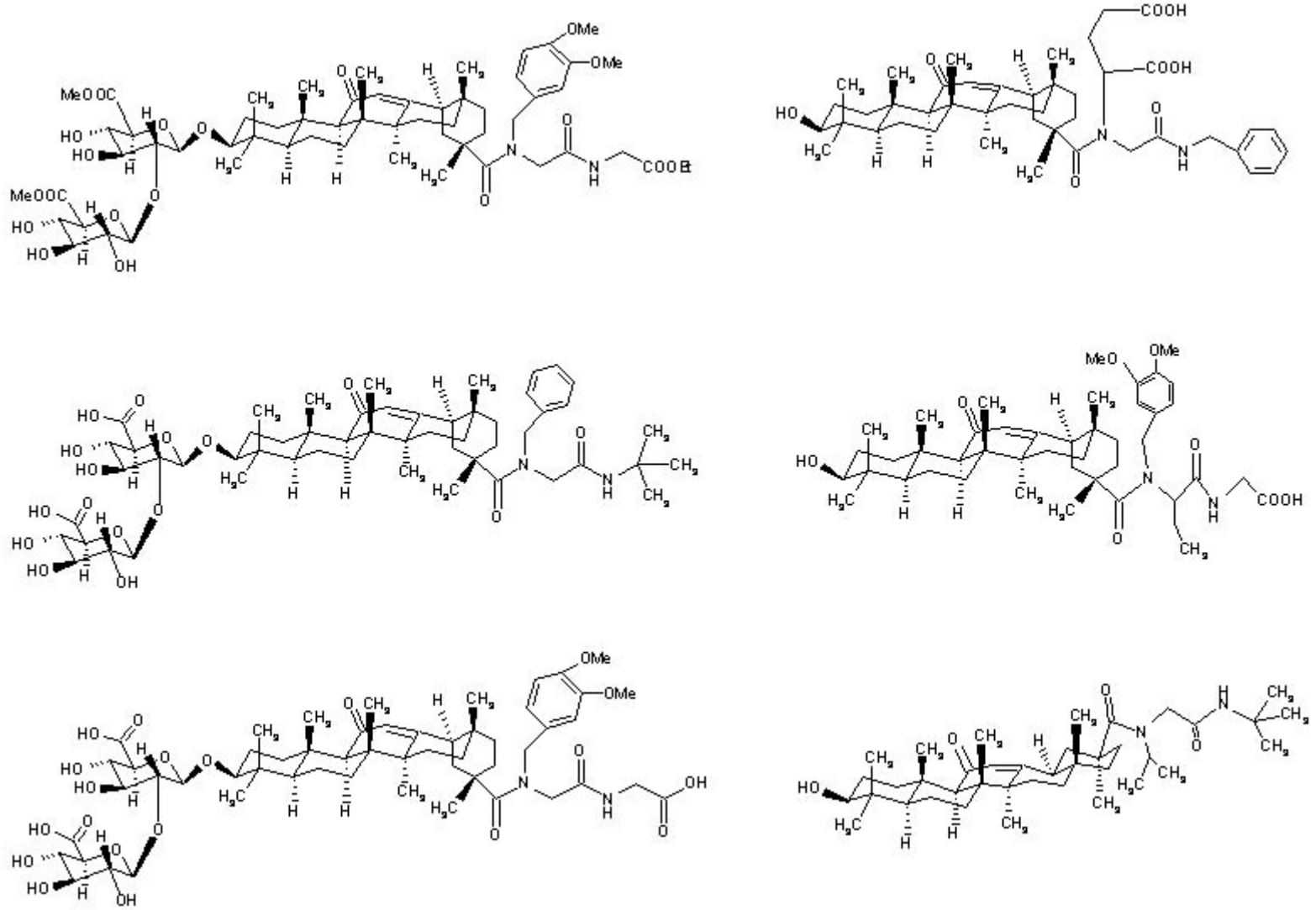
We employed both 18beta- and 18alpha-GHA as well as glycyrrhizin as acid component (Ac). Amines (Am), aldehydes (Ald) and isonitriles (In) were commercial available compounds.

The reactions were carried out for prolonged periods of times at room temperature in ethanol [6] and resulted in the formation of the desired compunds in 13-91% yield . A total 51 of compounds were prepared and fully characterized.



Typical product structures are shown in Fig. 1, and table 1 lists the compounds prepared. Glycyrrhizin and adamantane carboxylic acid were purchased from Sigma-Aldrich and 18ß-glycyrrhetinic acid from Across. 18alpha-glycyrrhetinic acid was synthesized using the method developed by Ullah et al [8].
By using formaldehyde as carbonyl component we received single pruducts. Other aldehydes result in a mixture of two diastereomeric compounds. Typical reaction times were 14 days at room temperature, in some cases acceptable yields were obtained only after 3-4 weeks reaction time. This result is comparible with a published report [9] that the Ugi reaction using sterically hindered components needed long reaction times, while higher temperatures result in the formation of complicated mixtures of products. Others solvents like THF, ethyl acetate or dichloromethane were tried but gave no advantage, mostly because of the low solubilty of the triterpene components. To increase solubility for biological testing potassium salts of the carboxylic acids were prepared.

Fig. 1. Typical members of the combinatorial library



In conclusion we described the successful use of sterically hindered triterpene carboxylic acids in the Ugi reaction thus demonstrating the potential to generate even large combinatorial libraries.

Experimental

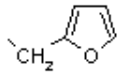
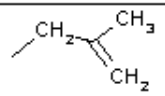
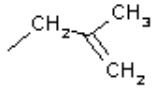
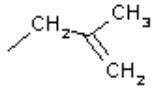
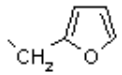
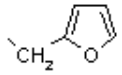
General procedure for UGI reactions

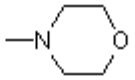
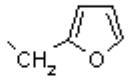
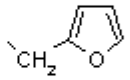
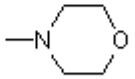
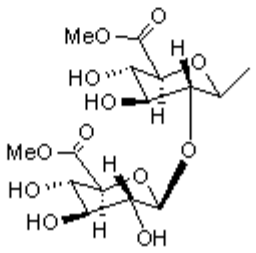
To a solution (or suspension in case of paraformaldehyde) of the aldehyde (1.0 mmol) in 15 mL dry ethanol 1.2 mmol of amine component was added and the mixture stirred under argon atmosphere stirred at room temp. for 1 h followed by the addition of the isocyanide (1.0 mmol) and acid (1.0 mmol) components. After stirring for 14 days at room temp. and regular control of the reaction progress by tlc the solvent was roto-evaporated, the residue dissolved in dichloromethane, the organic layer was washed with 1N HCl and with sat. NaHCO3 and with water. The org layer was separated, dried over MgSO4 and the solvent evaporated. The residue was purified over SiO2 with MDC and 0-5 % MeOH to give the UGI product.

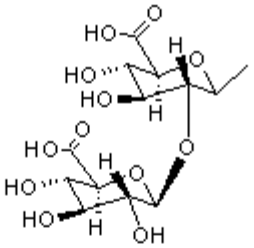
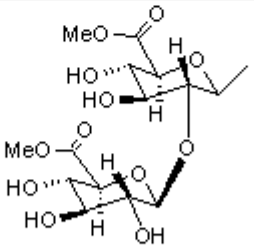
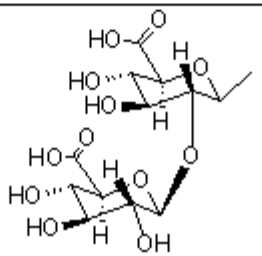
General procedure for ester hydrolysis

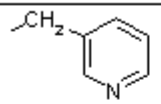
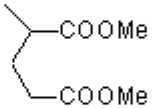
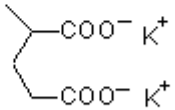
A solution of the corresponding ester dissolved in a mixture of methanol and THF was treated with 0.5 M KOH (1.01 eq.) and stirred at rt. The reaction was monitored by thin layer chromatography (CHCl3:MeOH=9:1). After complete hydrolysis of the ester (24 – 48 h) the solution was evaporated to dryness to afford the final product as fine powder.

Table 1: The synthesized 4CR Ugi products of triterpene

Nr	yield%	R_1	R_2	R_3	R	Pos 18
1	46		nPr	tert.-Bu	H	beta
2	24		H	tert.-Bu	H	beta
3	56	Me	H	tert.-Bu	H	beta
4	38		H	-CH_2-COOMe	H	beta
5	96*		H	-CH_2-COO^- K^+	H	beta
6	51	iPr	H	tert.-Bu	H	beta
7	58	nBu	H	-CH_2-COOMe	H	beta
8	99*	nBu	H	-CH_2-COO^- K^+	H	beta
9	14	Me	Et	tert.-Bu	H	beta
10	40	Bn	H	-CH_2-COOMe	H	beta
11	97*	Bn	H	-CH_2-COO^- K^+	H	beta
12	83		H	tert.-Bu	H	beta
13	49	Bn	Et	tert.-Bu	H	beta
14	33		Et	tert.-Bu	H	beta
15	72	All	H	tert.-Bu	H	beta
16	60	Bn	H	tert.-Bu	H	beta

17	24		H	tert.-Bu	H	beta
18	37	iPr	H	Ph	H	beta
19	80	3,4-dimethoxybenzyl	H	tert.-Bu	H	beta
20	68	iPr	H	tert.-Bu	H	alpha
21	11	Bn	H	tert.-Bu	H	alpha
22	30	$-CH_2-CH_2-OH$	H	$-CH_2-COOMe$	H	beta
23	98*	$-CH_2-CH_2-OH$	H	$-CH_2-COO^- K^+$	H	beta
24	40		H	$-CH_2-COOMe$	H	beta
25	95*		H	$-CH_2-COO^- K^+$	H	beta
26	53	iPr	H	$-CH_2-COOEt$	H	beta
27	97*	iPr	H	$-CH_2-COO^- K^+$	H	beta
28	33	Me	H	tert.-Bu	H	alpha
29	50		H	tert.-Bu	H	alpha
30	22	Bn	H	tert.-Bu		beta

31	60*	Bn	H	tert.-Bu		beta
32	47	-CH_2-COOEt	H	tert.-Bu	H	beta
33	97	-CH_2-COO^- K^+	H	tert.-Bu	H	beta
34	90	3,4-dimethoxybenzyl	H	-CH_2-COOEt	H	beta
35	98*	3,4-dimethoxybenzyl	H	-CH_2-COO^- K^+	H	beta
36	20	3,4-dimethoxybenzyl	Et	-CH_2-COOMe	H	beta
37	99*	3,4-dimethoxybenzyl	Et	-CH_2-COO^- K^+	H	beta
38	30	-CH_2-COOEt	H	-CH_2-COOEt	H	beta
39	98*	-CH_2-COO^- K^+	H	-CH_2-COO^- K^+	H	beta
40	13	3,4-dimethoxybenzyl	H	-CH_2-COOEt		beta
41	98*	3,4-dimethoxybenzyl	H	-CH_2-COOH		beta

42	13	All	Et	-CH_2-COOMe	H	beta
43	95*	All	Et	-CH_2-COO^- K^+	H	beta
44	62	iPr	H		H	beta
45	41	-CH_2-COOEt	H	Bn	H	beta
46	100*	-CH_2-COO^- K^+	H	Bn	H	beta
47	35		H	Bn	H	beta
48	95*		H	Bn	H	beta
49	92	iPr	H	Bn	H	beta
50	51	—CH_2-C≡CH	H	-CH_2-COOEt	H	beta
51	100*	—CH_2-C≡CH	H	-CH_2-COO^- K^+	H	beta

* yield of the hydrolysis of the ester group

Table 2: The synthesized 4CR Ugi products of adamantane carboxylic acid

Nr	yield %	R_1	R_2	R_3
52	30	3,4-dimetoxy benzyl	H	tert.-Bu
53	47	3,4-dimetoxy benzyl	H	$-CH_2-COOEt$

Antiviral screening

The results of the antiviral screening will be roported shortly.

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Acknowledgements

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