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Meldrum's Acid in Multicomponent Reactions: Applications to Combinatorial and Diversity-Oriented Synthesis

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Abstract

In a multicomponent reaction (MCR), one can create multiple new bonds in a single reaction from readily available starting materials; thus, MCRs are resource- and time-effective and therefore economically favorable processes in diversity generation. In contrast, there are MCRs where a multifunctional building block is introduced instead of an additional diversity-holding component, and these can be derivatized using very diverse reactions post-synthetically leading to novel chemotypes. The synthetic applications of Meldrum's acid are focusing primarily on reactions where it is applied as an alternative for acyclic malonic esters. However, its highly acidic character broadened its applications and made it a very useful reagent for MCRs or more precisely in tandem or domino reactions. There are numerous examples reported for the use of the alkylidene conjugates of Meldrum's acid as dienophiles in hetero-Diels–Alder reactions, as well as Michael acceptors. In most cases spontaneous or concomitant post-synthetic derivatization increased its synthetic utility. This minireview gives a non-exhaustive insight into MCRs involving Meldrum's acid, describing various applications in combinatorial and diversity-oriented synthesis.

1 Introduction

Multicomponent Reactions (MCRs) have been a versatile tool for synthetic chemists in the preparation of structurally diverse compounds. MCRs comprise reactions with more than two reactants and the newly formed product contains atoms of each precursor [1]. In contrast, the probability that three or more molecules collide in the right direction and at the appropriate energy level is very low, most of the known MCRs could be considered more precisely as domino or tandem reactions. MCRs are resource- and time-effective, and therefore economically favorable processes; thus, a vast number of diverse compounds can be obtained in a parallel synthesis [2]. In recent years, there has been a growing interest in MCRs in the chemical and pharmaceutical industries, as MCRs not only lower production costs due to their high convergence and atom efficiency, but also reduces the environmental burden, which is the major principle of green chemistry.

The enormous synthetic possibilities that MCRs offer can be further increased by post-synthesis transformations, which can be furnished by concomitant reaction of a suitably functionalized or protected MCR product. These modifications can be either spontaneous reactions with the medium, intramolecular rearrangements, or can take place upon treatment with additional reagents.

Meldrum's acid (**1**) described first by A. N. Meldrum [3] is a white crystalline solid that can be easily prepared by the condensation of malonic acid and acetone in acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid [4]. Meldrum's acid shows several unique features. It has an unusually high acidity [5]; the pK_a of Meldrum's acid in DMSO is 7.325, but those of dimedone and dimethyl malonate, corresponding to the cyclic diketone and acyclic ester analogues, are 15.87 and 11.16, respectively.

Furthermore, it is susceptible to electrophilic attack at C5 and nucleophilic attack at C4 and C6. Additionally, its unique ring-opening reactions make it a tremendously attractive and useful building block. The synthetic applications of Meldrum's acid are focusing primarily on reactions where it is applied as an alternative for acyclic malonic esters, but there are numerous examples reported for the use of the alkylidene conjugates of Meldrum's acid as dienophiles in hetero-Diels–Alder reactions. In most cases spontaneous or concomitant post-synthetic derivatization increases its synthetic utility. The MCRs involving Meldrum's acid generally retain the unique ring-captured

malonic acid moiety, which can be released by loss of acetone, when reacting with nucleophiles. This reaction is frequently accompanied with partial decarboxylation. In this way various diversity elements can be built into the diverse MCR products. Frequently, nucleophiles in appropriate proximity could intramolecularly attack the cyclic acetonide fragment, leading to unique ring systems, which can be used in Diversity-Oriented Synthesis (DOS) [6].

Based on the above findings, the MCRs involving Meldrum's acid belong to those classes where it participates as a multifunctional building block in the reaction instead of one diversity-holding component, so the MCR product can be further derivatized in a large variety of reactions leading to diverse skeletons or chemotypes.

Corresponding to the initial step and the primary intermediate formed involving Meldrum's acid, the MCRs can be classified into various subgroups. In most cases, a reactive alkylidene Meldrum's acid intermediate (a Knoevenagel adduct) participates in various secondary reactions. This two-step feature is reflected, in many cases, in the name of MCRs involving Meldrum's acid [domino Knoevenagel – Diels – Alder, domino Wittig – Knoevenagel – Diels – Alder, modified Hantzsch reaction, Yonemitsu reaction (domino Knoevenagel – Michael reaction), *etc.*]. In most of the above cases Meldrum's acid, condensed first with carbonyl moieties, could ultimately lead to a substituted propionic acid extension of the molecules. Domino Knoevenagel-isonitrile-cycloaddition represents a unique subclass, since the major product retains both carboxylic groups of the masked malonic acid moiety.

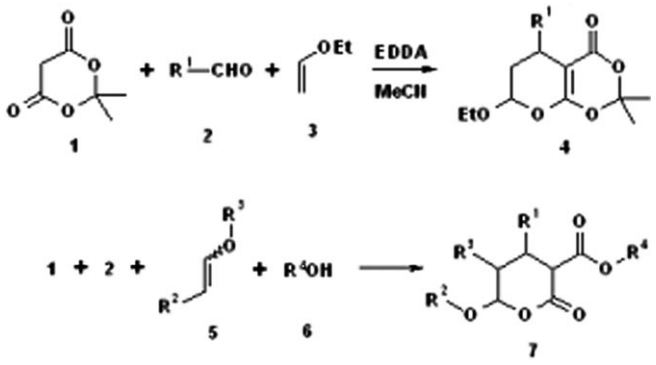
Some MCRs cannot be clearly classified where, for example, Meldrum's acid reacts with unsaturated carbonyl compounds in a Knoevenagel condensation and ring closure is followed by condensation. In other cases Meldrum's acid acts as a Michael donor with its highly acidic methylene moiety in an aldol-type reaction.

In the present minireview we follow this classification providing a general description and examples to each subclass.

2 Domino Knoevenagel-hetero-Diels – Alder Reactions

2.1 Diversity-Oriented Alkaloid Synthesis

In the reactions involving Meldrum's acid (**1**), an aldehyde (**2**), and a vinyl ether derivative (**3**) – that can be considered as a domino Knoevenagel-hetero-Diels – Alder reaction (Scheme 1) – in the presence of EDDA (Ethylene Diammonium Acetate) the initial step is a Knoevenagel condensation between the aldehyde and Meldrum's acid. In the second step the previously formed alkylidene Meldrum's acid, as a hetero-diene, undergoes a Diels – Alder reaction with the dienophile present [7].



Scheme 1. Three- and four-component domino Knoevenagel – hetero-Diels – Alder reactions.

If the transformation is performed in alcohol then the cyclic acetonide ring is cleaved, yielding the lactone ester **7** (Scheme 1).

In the following examples, the application of the three-component domino Knoevenagel-hetero-Diels – Alder reaction is shown in the synthesis of alkaloids, such as (−)-hirsutine **8**, (+)-dihydrocorynantheine **9**, dihydroantirhin **10**, emetine **11,** and tubulosine **12** (Figure 1).

Hirsutine **8**, a corynanthe indole alkaloid, showed a significant inhibitory effect on the influenza A virus [8]. The enantiopure *Z*-protected amino aldehyde (*R*)-**13** was reacted with **1** and with enolether **15** in the presence of EDDA to obtain lactone **17** *via* the Knoevenagel product **14** and loss of carbon dioxide and acetone. The ratio of the diastereomers was better than 24 : 1 for the preferred epimer. The solvolysis of the lactone ring gave the corresponding hemiacetal, which spontaneously transformed to aldehyde **18** by methanol elimination. After removal of

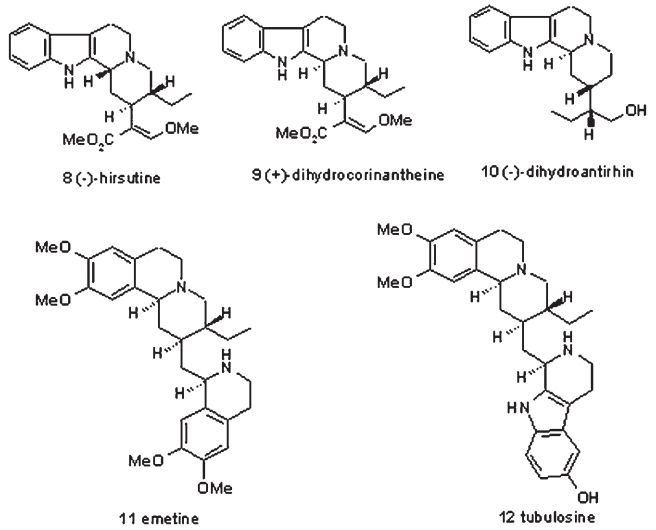
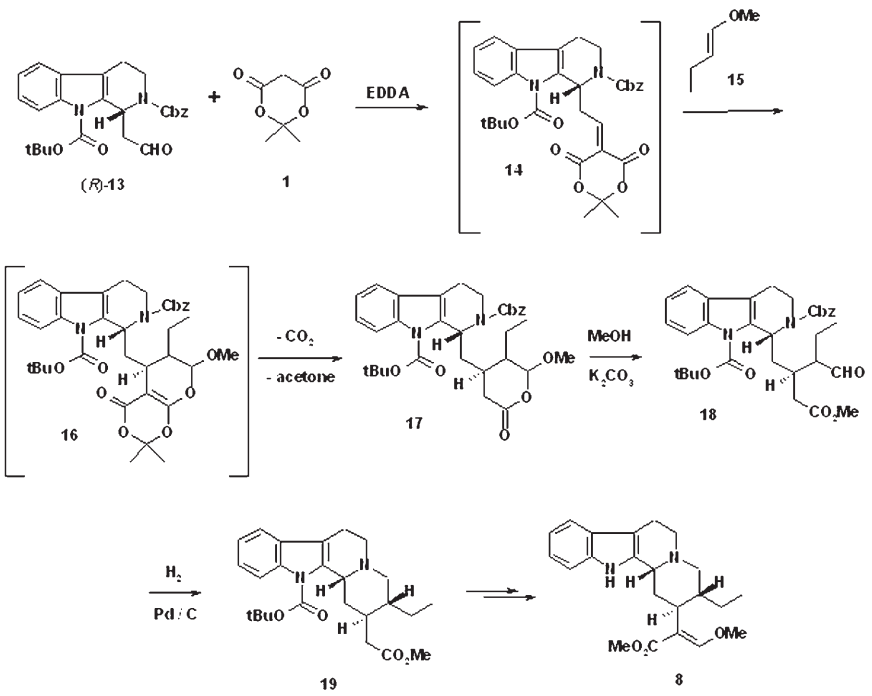


Figure 1. Alkaloids synthesized by a three-component domino Knoevenagel – hetero-Diels – Alder reaction.



Scheme 2. Synthesis of (−)-hirsutin **8.**

the Cbz group an intramolecular ring closure took place followed by the double-bond saturation giving quinolizidine **19.** Removal of the Boc-group, condensation with methyl formate, and methylation of the corresponding enol resulted in hirsutine **8** (Scheme 2) [9].

The synthesis of (+)-dihydrocorinantheine **9** [10], the 3-epimer of hirsutine **8**, followed a route similar to the synthesis of hirsutine **8**, albeit with a lower diastereoselectivity [11].

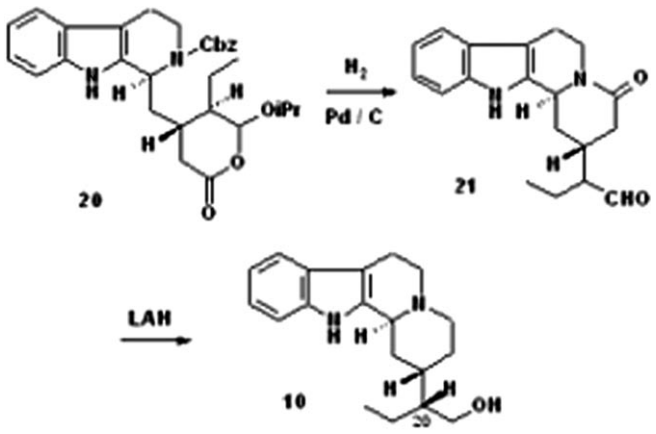
The same synthetic approach was used for the synthesis of (−)-dihydroantirhin **10** [11], a vallesiachotamine-type alkaloid, where the Cbz-group of **20** was removed by hydrogenolysis and the resulting secondary amine attacked the lacton moiety to form the lactam- and aldehyde-containing **21.** Reduction of the amide and aldehyde functions gave dihydroantirhin **10**, which contained 10% of the 20-epimer (Scheme 3).

The synthesis of emetine **11** [12] and tubulosine **12** [13] was also solved with the same synthetic strategy starting from the optically active tetrahydroisoquinoline derivative **22** (Scheme 4). Without the isolation of the resulting lactone **24**, it was treated with potassium carbonate, methanol, and a catalytic amount of palladium on charcoal, first under a nitrogen atmosphere and then under hydrogen atmosphere to give the desired benzoquinolizidine **25** together with its diastereomers. After separation of the diastereomers, **25** was used for the synthesis of emetine **11** and tubulosine **12** *via* the amidation with phenylethylamine **26** or triptamine derivative **27**, respectively, followed by a Bischler–Napieralski ring closure and an enantioselective transfer hydrogenation.

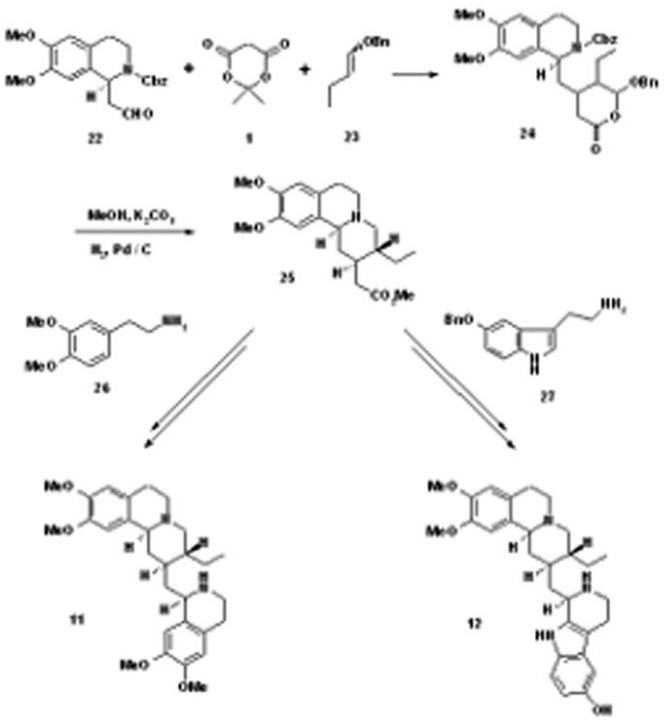
2.2 Domino Knoevenagel-Pseudo-Hetero-Diels–Alder Reaction

A proline-catalyzed enantioselective three-component reaction between ketones, aldehydes, and Meldrum's acid was first described by List and Castello (Scheme 5) [14]. The enantioselectivity of these reactions was rather low; however, using cyclic ketones the products (**29a-d**) were obtained as single diastereomers.

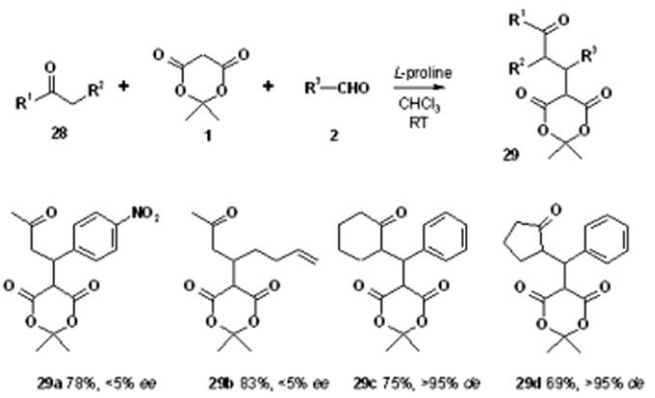
The authors proposed a domino Knoevenagel-hetero-Diels–Alder reaction mechanism where proline acts as a catalyst for both the iminium ion and enamine formation (Scheme 6). Formally the reaction could be determined as a domino Knoevenagel–Michael reaction.



Scheme 3. Synthesis of (−)-dihydroantirhin **10.**



Scheme 4. Syntheses of emetine **11** and tubulosine **12.**



Scheme 5. Organocatalytic domino Knoevenagel – pseudo-hetero-Diels – Alder reaction.

In Scheme 7, a related organo-catalyzed reaction is shown using a benzylidene acetone derivative **30** as the diene component. The reaction is catalyzed by proline or 5,5-dimethylthiazolidine-4-carboxylic Acid (**31**, DMTC). Barbas and co-workers [15] – using enantiopure proline or DMTC – investigated the enantioselectivity, as well as its dependence on the different dielectric constant of the solvent. The best result was achieved using DMTC in methanol, which produced **32a** in 93% yield and 99% *ee*.

The authors proposed a mechanism for the reaction that proceeds *via* a Knoevenagel condensation between Meldrum's acid and the aldehyde, followed by the Diels – Alder reaction of the aralkylidene Meldrum's acid with the *in situ* formed dieneamine through the reaction of the enone with the chiral amine catalyst.

3 Domino Wittig – Knoevenagel-Pseudo-Diels – Alder Reaction

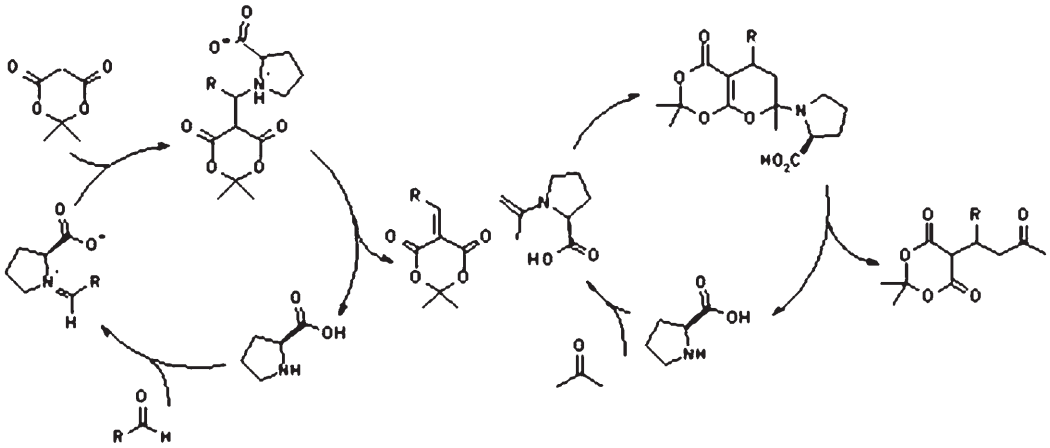
The same product can be obtained under identical conditions when the benzylidene acetone derivative is formed *in situ* by a proline-catalyzed aldol reaction of acetone with another equivalent of the aldehyde (Scheme 8) [16]. In this case two competing reactions can be envisaged. *Pseudo* four-component domino aldol-Knoevenagel – Diels – Alder reaction leads to spiro product **32**, while domino Knoevenagel – hetero-Diels – Alder reaction yields the corresponding List – Castello product **29.** To avoid the formation of the byproduct **29,** a new reaction sequence was developed using a Wittig – Knoevenagel-Diels – Alder reaction sequence, starting from 1-(triphenylphosphanylidene)-propan-2-one (**34**), Meldrum's acid, and benzaldehyde, giving exclusively spiro product **32** with high yield and excellent diastereomeric ratio [16].

4 Modified Hantzsch Synthesis

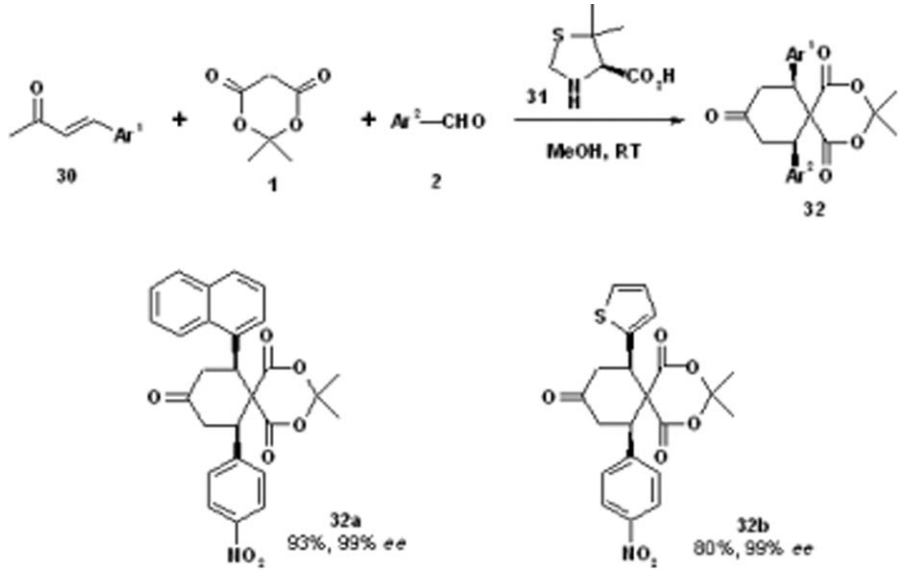
In the presence of a base, Meldrum's acid readily reacts with electrophilic olefins *via* Michael addition leading to its functionalized alkyl derivatives. The reaction of Meldrum's acid with 4-(2-hydroxyphenyl)but-3-en-2-one (**35**) in the presence of ammonium acetate gave oxygen-bridged tetrahydro-2-pyridone **37** (Scheme 9) [17]. The formation of the product can be assumed as a Michael addition between Meldrum's acid and the unsaturated ketone, followed by an aminal formation and an intramolecular nucleophilic attack of the nitrogen atom at the dioxanedione ring of **36.**

The same research group applied Meldrum's acid as a second dicarbonyl component in the Hantzsch reaction to obtain 1,2,3,4-tetrahydro-pyridin-2-ones (**39**) [17] as precursors of 4,7-dihydro-1*H*,3*H*-furo[3,4-*b*]pyridine-2,5-diones **(40)** or 4,7-dihydro-1*H*-pyrazolo[3,4-b]pyridines **(41)** (Scheme 9) [18]. The key intermediate is a typical Knoevenagel adduct with the aromatic aldehyde.

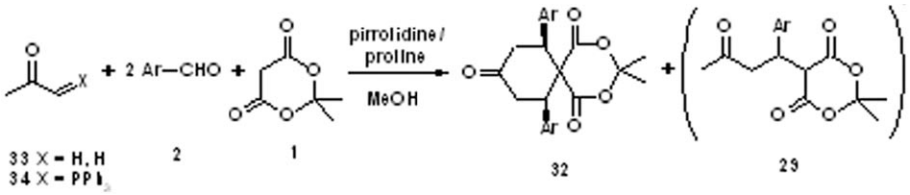
Recently, based on the above reaction, we have prepared a 2000-member 3,4-dihydro-1*H*-pyridin-2-one library with potential activity against Benign Prostatic Hyperplasia (BHP) (Scheme 10). We found that the reaction works only with aromatic aldehydes and ketoesters having a methylene group at the carbonyl terminal. The alkylation was performed with active alkylating agents (**42a – c**) in dry DMF using potassium *t*-butoxide as base in order to reduce the formation of the O-alkylated product. The ester moiety on the Dihydropyridine (DHP) ring was resistant to hydrolytical conditions; thus, it allowed us to hydrolyze selectively the ester group exclusively on the spacer.



Scheme 6. Mechanism of the organocatalytic domino Knoevenagel – pseudo-hetero-Diels – Alder reaction.



Scheme 7. Enantioselective domino Knoevenagel – hetero-Diels – Alder reaction using DMTC catalyst.

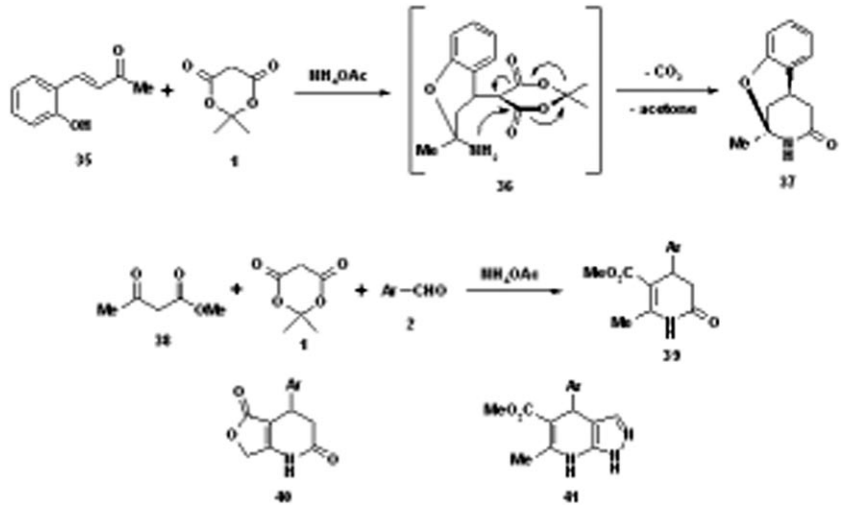


Scheme 8. Domino aldol/Wittig – Knoevenagel-pseudo-Diels – Alder reaction.

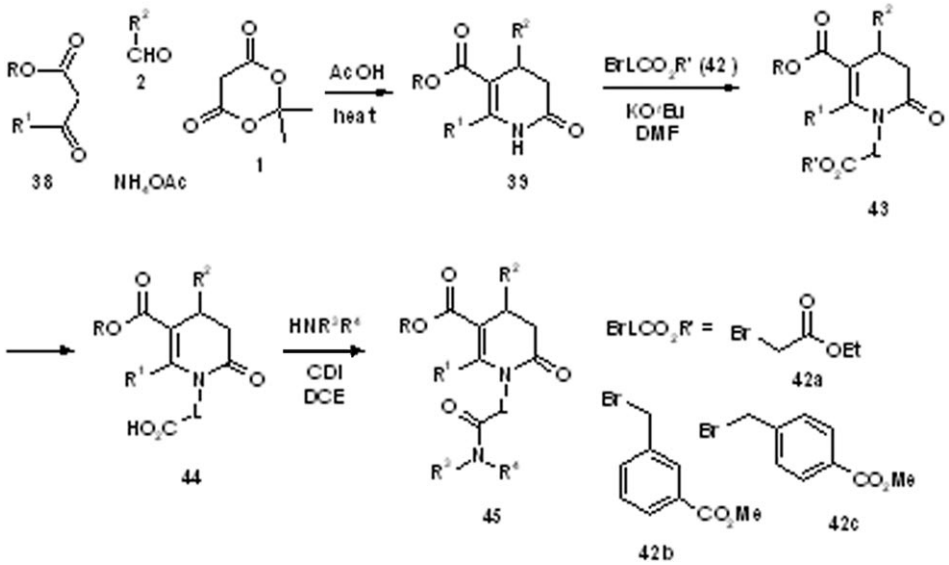
The amidation of **44** was performed in 1,2-dichloroethane (DCE) using 1,1′-carbonyldiimidazole (CDI) as activating agent [19].

5 Alkylidene Meldrum's Acid Precursors

Eberle and Lawton described a reaction between Meldrum's acid, aldehydes, and thiophenol in the presence of piperidinium acetate in acetonitrile giving phenylthio-protected alkylidene Meldrum's acid derivatives **47** [20]. The mechanism of the reaction can be considered as a domino



Scheme 9. The modified Hantzsch synthesis.



Scheme 10. Solution-phase parallel synthesis of tetrahydro-pyrimidone library based on the modified Hantzsch synthesis.

Knoevenagel – nucleophilic-addition reaction. Due to the fact that these species are solid, easy-to-isolate, and stable substances, in contrast to the alkylidene derivatives of Meldrum's acid, their phenylthio-protected derivatives are advantageous. The reactions of **47** as alkylidene Meldrum's acid precursors proceed through thiophenol elimination. The versatility of compound **47** is demonstrated in Scheme 11.

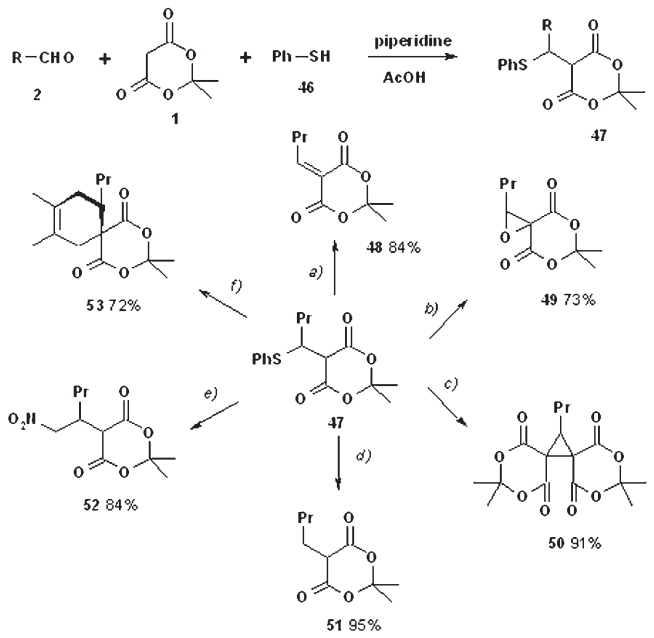
The same versatility can be achieved if thiocarboxylic acid **54** is used instead of thiophenol obtaining the thioacyl-protected alkylidene Meldrum's acid derivatives (**55**) (Scheme 12) [20].

Zia-Ebrahimi and Huffman reported the synthesis of a novel methylene Meldrum's acid precursor (Scheme 13) *via* the three-component reaction of Meldrum's acid **1**, aqueous formaldehyde **64**, and pyridine [21]. The subsequent pyridine adduct **65** proved to be a stable source of methylene Meldrum's acid and in the synthesis of γ-carboxyglutamic acid showed advantages over the classical methods.

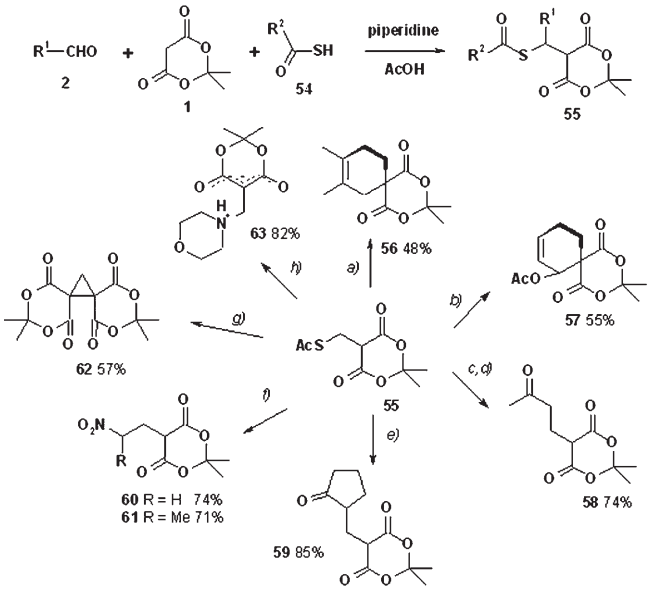
Practically, alkylidene Meldrum's acids represent versatile precursors for various unique scaffolds and building blocks.

6 The Yonemitsu Reaction (Domino Knoevenagel – Michael)

Yonemitsu and co-workers reported a proline-catalyzed three-component domino Knoevenagel – Michael reaction

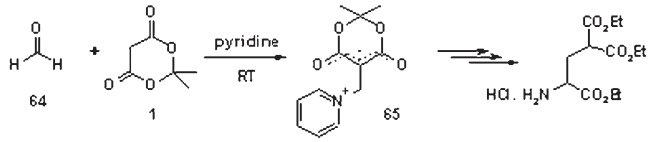


Scheme 11. Alkylidene Meldrum's acid precursors as versatile reagents. a) $K_3[Fe(CN)_6]$, KOH. b) H_2O_2, MeCN. c) Meldrum's acid, $NaIO_4$, MeCN/H_2O. d) $NaBH_4$, THF/EtOH. e) $MeNO_2$, Bu_4NOH, MeOH/THF. f) 2,3-Dimethyl-1,3-butadiene, DCM.



Scheme 12. Alternative alkylidene Meldrum's acid precursors. a) 2,3-Dimethyl-1,3-butadiene, DMSO. b) 1,3-Butadienyl acetate, DMSO. c) 2-Methoxypropene, K_2CO_3, MeCN. d) H^+. e) Morpholinocyclopentanone enamine, MeCN. f) RCH_2NO_2, Bu_4NOH, THF. g) Meldrum's acid, $NaIO_4$, MeCN/H_2O. h) Morpholine, MeCN.

between Meldrum's acid, indole, and aldehydes [22]. Subsequent decarboxylation and ethanolysis of **67** led to ethyl 3-substituted (indol-3-yl)-propionates **68**, used as intermediates in the synthesis of indole alkaloids [23]. Sapi and Laronze examined thoroughly the nature of the so-called Yonemitsu reaction and reported several papers on its useful application toward carbolines (**69**), unusual tryptophans (**70**), tryptamines (**71**), and indole heterocycles (**72**) [24], thus extending it toward DOS (Scheme 14).



Scheme 13. Methylene-Meldrum's acid precursor.

They also extended the reaction to 2-substituted indoles (**73**) and, by altering the reaction conditions, a variety of new scaffolds (**74**–**77**) were obtained (Scheme 15) [25].

We also successfully applied the Yonemitsu reaction to produce a diverse indol-3-propionic acid amide compound library [26] using the synthetic protocol originally developed by Yonemitsu and co-workers. Moreover, we successfully extended the reaction from indoles to imidazo[1,2-*a*]pyridines (**78**) and utilized this reaction to produce an "azalogue" imidazo[1,2-*a*]pyridine-3-yl-propionic acid amide **82** library (Scheme 16) [27].

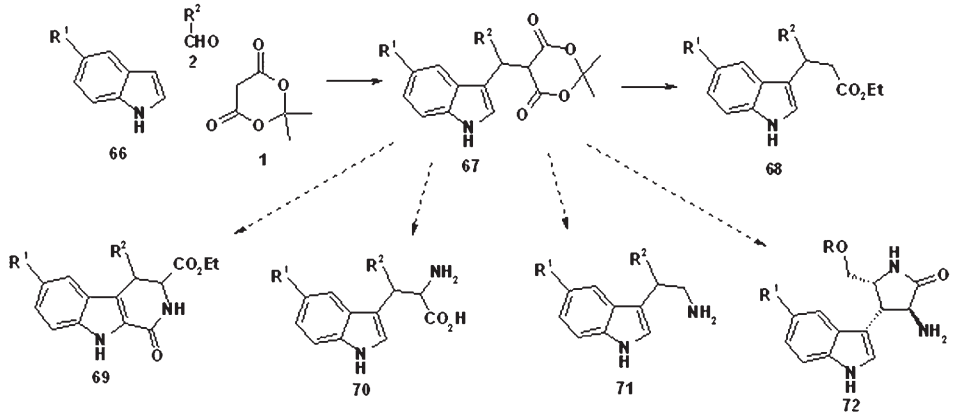
7 Domino (Knoevenagel) – Cycloaddition-Solvolysis – I-MCR (Isonitrile-MCR)

The condensation product of Meldrum's acid and 4-nitrobenzaldehyde (Knoevenagel adduct **83**) reacts smoothly with alkyl isonitriles (**84**) in the presence of alcohols to give 2-[1-*p*-nitrophenyl-2-(alkylamino)-2-oxoethyl]malonates (**85**) (Scheme 17) [28]. The authors propose two possible mechanisms for the reaction; however, the fact that the reaction works well with *tert*-butanol as the alcohol component makes pathway B more likely.

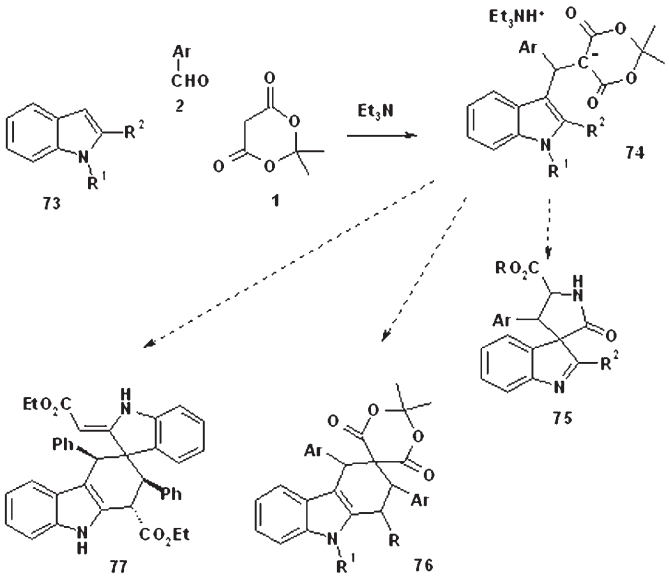
8 Biginelli-like Reaction

Shaabani *et al.* reported the utilization of Meldrum's acid in a pseudo four-component Biginelli-like reaction giving σ symmetric spiro heterobicyclic rings **93** (Scheme 18) [29]. The reaction proceeds smoothly with electron-withdrawing *para*-substituted benzaldehydes without any solvent and catalyst, but when applying electron-donating *para*-substituted derivatives only the Knoevenagel adducts could be isolated. The classical Biginelli product **94** could not be isolated in any of the cases.

Although the mechanism of the reaction has not been proved yet, the authors offer two reasonable pathways (Scheme 19). Along Pathway A, the addition of urea **92** to



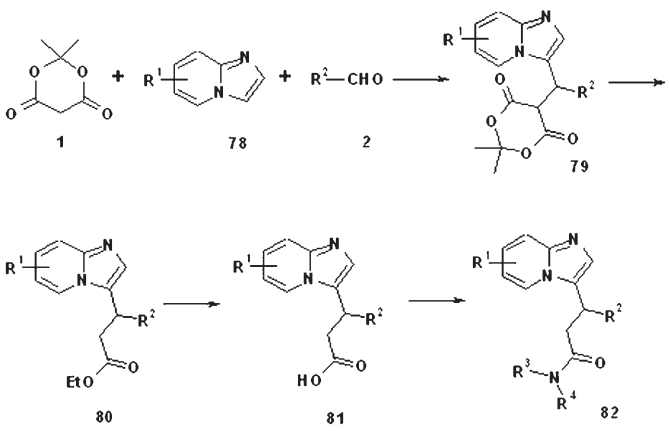
Scheme 14. The application of the Yonemitsu reaction in the synthesis of various indole derivatives.



Scheme 15. Yonemitsu reaction of 2-substituted indoles.

aldehyde **91** leads to highly reactive *N*-acylimine derivative **95**, which readily proceeds with Meldrum's acid in a Michael reaction giving ureide **96**, to which a second aldehyde is added to produce *N*-acylimine intermediate **97.** Subsequently, intermediate **97** cyclizes to the spiro compound **93.**

Along Pathway B, a standard Knoevenagel condensation is assumed between Meldrum's acid and the aldehyde, followed by a Michael-type addition of the urea furnishing ureide **96**, which reacts with another molecule of aldehyde and immediately cyclizes to the spiro compound **93.** Not only benzaldehydes with electron-donating substituents decrease the reaction rate in both mechanisms A and B, but also the Michael-type addition of urea to electron-rich aralkylidene Meldrum's acid is inhibited. Due to the fact that the reaction proceeds with benzaldehydes containing electron-donating substituents in the *para* position only up to the Knoevenagel adducts **98**, Pathway B is expected to be more probable, thus proceeding through a domino Knoevenagel – Michael reaction sequence.

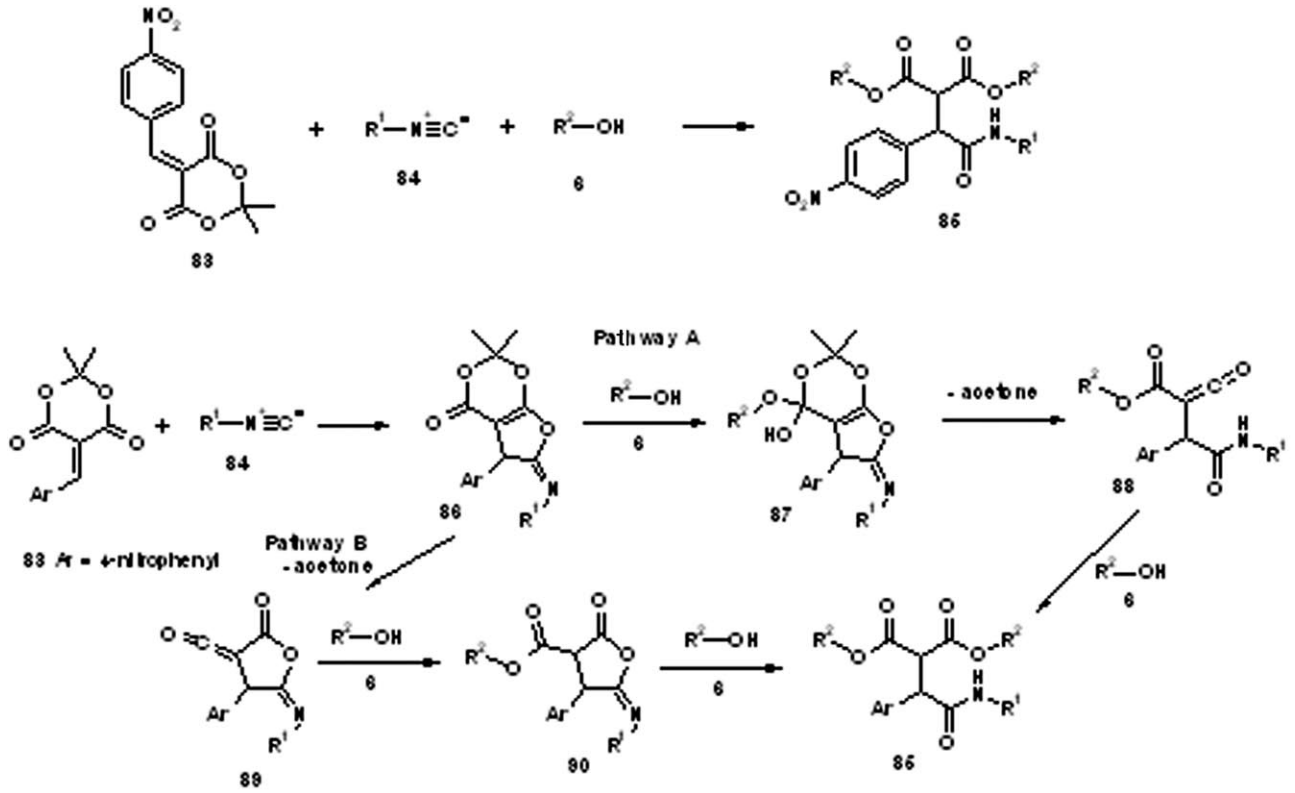


Scheme 16. Extension of the Yonemitsu reaction to imidazo[1,2-a]pyridines.

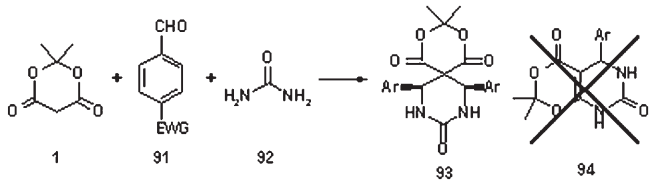
9 Summary and Conclusion

Even though in this non-exhaustive account we described several diverse applications there are still unexploited areas regarding the application of Meldrum's acid in MCRs.

Several of the reactions are still not adapted to parallel synthesis producing large combinatorial libraries; thus, parameter optimization and chemical evaluation are still required to identify which building blocks are suitable for high-throughput synthesis. Interestingly, no examples were reported using solid-phase synthesis or applying polymer-supported reagents. In conclusion, Meldrums's acid still provides much room for the creativity of synthetic chemists studying the diverse modification of the MCR adducts



Scheme 17. An I-MCR involving Meldrum's acid.



Scheme 18. Biginelli-like reaction with Meldrum's acid.

concomitantly or post-synthetically. This holds the promise of increasing both skeletal and fragmental diversity.

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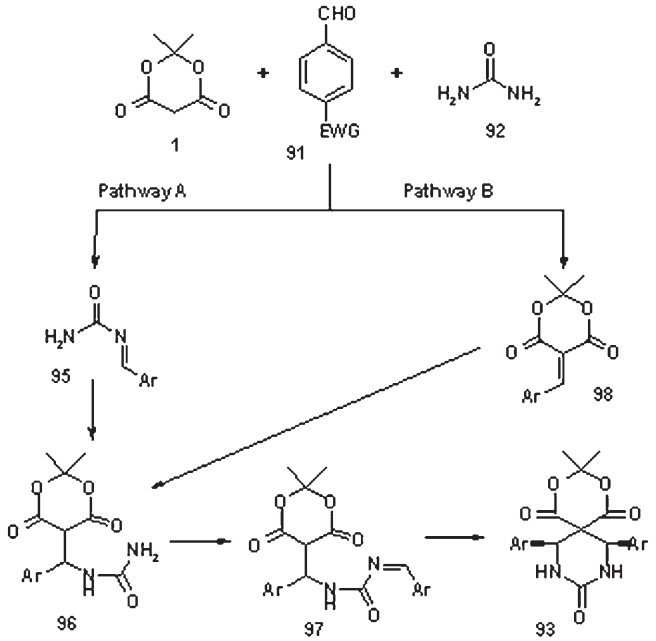

Scheme 19. Possible mechanism pathways for the Biginelli-like reaction.

References

[1] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18(3)*, 115.
[2] B. Beck, A. Dömling, S. Hess, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1701.
[3] A. N. Meldrum, *J. Chem. Soc.* **1908**, *93*, 598.
[4] D. Davidson, S. A. Bernhardt, *J. Am. Chem. Soc.* **1948**, *70*, 3426.
[5] E. M. Arnett, J. A. Harrelson, *J. Am. Chem. Soc.* **1987**, *109*, 809.
[6] Y. Liao, Y. Hu, J. Wu, Q. Zhu, M. Donovan, R. Fathi, Z. Yang, *Curr. Med. Chem.* **2003**, *10(21)*, 2285.
[7] L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, *20*, 304.
[8] H. Takayama, Y. Iimura, M. Kitajima, N. Aimi, K. Konno, H. Inoue, M. Fujiwara, T. Mizuta, T. Yokota, S. Shigeta, K. Tokuhisa, Y. Hanasaki, K. Katsuura, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3145.
[9] L. F. Tietze, Y. Zhou, *Angew. Chem.* **1999**, *111*, 2076; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2045.
[10] D. Staerk, E. Lemmich, J. Christensen, A. Kharazmi, C. E. Olsen, J. W. Jaroszewski, *Planta Med.* **2000**, *66*, 531.
[11] L. F. Tietze, J. Bachmann, J. Wichmann, Y. Zhou, T. Raschke, *Liebigs Ann./Recueil*, **1997**, 881.
[12] A. Itoh, Y. Ikuta, Y. Baba, N. Tanahashi, N. Nagakura, *Phytochemistry* **1999**, *52*, 1169.
[13] A. Itoh, Y. Ikuta, N. Tanahashi, N. Nagakura, *J. Nat. Prod.* **2000**, *63*, 723.
[14] B. List, C. Castello, *Synlett* **2001**, 1687.
[15] D. B. Ramachary, N. S. Chowdari, C. F. Barbas, *Angew. Chem.* **2003**, *115*, 4365; *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4233.
[16] D. B. Ramachary, C. F. Barbas, *Chem. Eur. J.* **2004**, *10*, 5323.
[17] J. Svetlik, I. Goljer, F. Turecek, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1315.
[18] Y. Verdecia, M. Suarez, A. Morales, E. Rodriguez, E. Ochoa, L. Gonzalez, N. Martin, M. Quinteiro, C. Seoane, J. L. Soto, *J. Chem. Soc., Perkin Trans. 1* **1996**, 947.
[19] Á. Bucsai, T. Nagy, F. Darvas, unpublished results.
[20] M. Eberle, G. Lawton, *Helv. Chim. Acta* **1988**, *71*, 1974.
[21] M. Zia-Ebrahimi, G. W. Huffman, *Synthesis* **1996**, 215.
[22] a) Y. Oikawa, H. Hirasawa, O. Yonemitsu, *Tetrahedron Lett.* **1978**, *20*, 1759; b) Y. Oikawa, H. Hirasawa, O. Yonemitsu, *Chem. Pharm. Bull.* **1982**, *30*, 7437.
[23] Y. Oikawa, M. Tanaka, H. Hirasawa, O. Yonemitsu, *Chem. Pharm. Bull.* **1981**, *29*, 1606.
[24] J. Sapi, J-Y. Laronze, *Arkivoc, vii*, 208, and references therein
[25] F. Cochard, M. Laronze, P. Sigaut, J. Sapi, J-Y. Laronze, *Tetrahedron Lett.* **2004**, *45*, 1703.
[26] T. Nagy, F. Darvas, unpublished results.
[27] J. Gerencsér, G. Panka, T. Nagy, O. Egyed, G. Dormán, L. Ürge, F. Darvas, *J. Comb. Chem.* **2005**, *7*, 530.
[28] A. Shaabani, I. Yavari, M. B. Teimouri, A. Bazgir, H. R. Bijanzadeh, *Tetrahedron* **2001**, *57*, 1375.
[29] A. Shaabani, A. Bazgir, H. R. Bijanzadeh, *Mol. Diversity* **2004**, *8*, 141.

