Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Enzymatic Kinetic Resolution of Internal Propargylic Diols. Part I: A New Approach for the Synthesis of *(S)*-Pent-2-yn-1,4-diol, a Natural Product from *Clitocybe catinus.*

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jeiely G. Ferreira[a], Cleverson R. Princival[b], Dyego M. Oliveira[a], Renata X. Nascimento[a], Jefferson L. Princival[a]*

Internal bis-substituted propargylic diols were subjected to enzymatic kinetic resolution promoted by CAL-B. Employing a two rounds sequence EKR, mono- and bis-acetoxy propargylic products were obtained in high enantiomeric ratio (*E*>200). The efficiently resolved chiral 8b was applied in a concise synthesis of (S)-1b, an optically active natural product produced by fungi *Clitocybe catinus*.

Introduction

Optically active alkynylic diols are subunits frequently found in polyacetylenic natural products[1] and their preparation has been increasingly conducted by synthetic chemists[2] due to the wide range of biological activity these compounds possess. Enantiomerically pure propargylic alcohols are well known, useful chiral building blocks in organic synthesis, owing to the versatility of the alkyne moiety which is readily converted into other functional groups. Examples include allenols,[3] furanones[4] and butenolides[5] which are very useful classes of chemicals in organic synthesis and can display a wide variety of biochemical and ecological functions. Despite bis-substituted propargylic diols often being important bioactive compounds, no systematically attempts have been made to establish a chemo enzymatic route for their preparation. It is noteworthy that in nature they are found in their enantiomerically pure forms, often as subunits of smaller or more complex molecules. Examples are compounds **1-3**, fungal metabolites produced by *Clitocybe catinus*[6] found in their enantiomerically pure form, and Osirisyne A(l) (**4**), an optically active polyacetylenic compound from sponge *Haliclonaosiri* (Chalinidae)[7] $[\alpha]_D^{25}$ = +11.8 (c 0.15, MeOH) for which the absolute stereochemistry has not yet been determined (Figure 1).

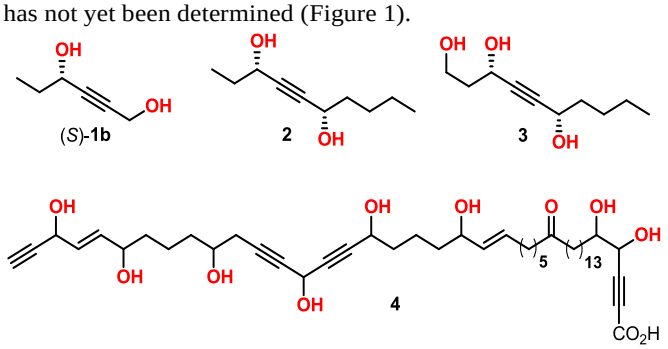


Fig. 1 Natural Alkynylic metabolites

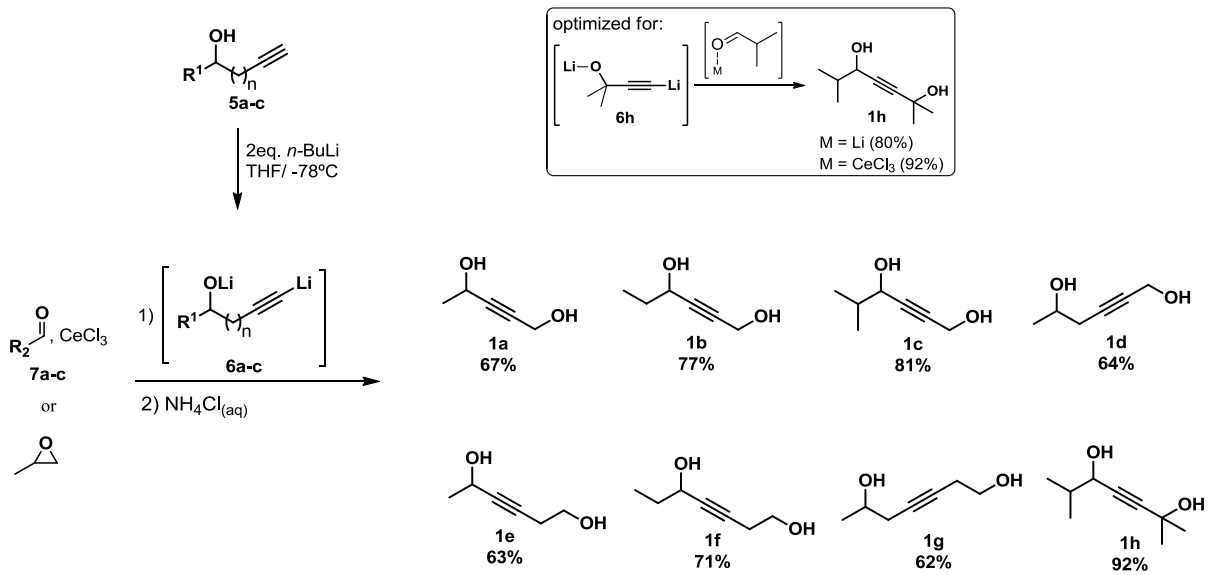
One of the most common enzymatic approaches to prepare simple asymmetric propargylic alcohols is to subject alcohols to a kinetic resolution using lipases either as free enzymes[8] or immobilized on a solid support.[9] Alternatively, they can be prepared by subjecting alkynones to the bioreduction promoted by alcohol dehydrogenases[10] or activated alkynes to α-hydroxylation using Chloroperoxidases.[11] However, to the best of our knowledge, no chemo enzymatic approach employing internal alkynylic diols in resolution studies has been reported to date. Hence, our aim is to establish a greener and enantioselective method of preparation, in small to large-scale, of enantiopure propargylic and homo propargylic diols, including the natural optically active compound **1b**. In order to achieve this goal we decided to investigate the enzymatic kinetic resolution of racemic propargylic diols catalysed by *Candida antarctica* Lipase B (CALB), a lipase that has proved to be a useful biocatalyst in organic solvents.

Results and discussion

Starting from the commercially available propargylic alcohols **5**, the synthesis of racemic diols were accomplished by a modified literature procedure.[12] With this the propargylic and homo propargylic alcohols were submitted to react with two equivalents of *n*-butyl lithium, followed by addition of a suitable electrophile. The respective bis-lithium salts generated *in situ* were reacted with aldehydes and propylene oxide, leading to the formation of the expected diols in moderate isolated yields. However, after the addition of a catalytic amount of the highly oxophilic metal salt cerium chloride (10 mol%), the desired products from the 1,2-addition reactions were obtained in slightly improved yields. Is important to highlight that the use of the free alcohol to prepare the bis-lithium salts **6** furnishes the desired products in better overall yields compared to the use of TMS or THP ether protecting group strategies which require additional steps. The synthetic route to propargylic diols **1a-h** is summarised in Scheme 1.

Journal Name RSCPublishing

ARTICLE



Scheme 1. Synthesis of racemic propargylic diols **1a-h**.

The same procedure ($CeCl_3$ 10 mol%) was employed using propylene oxide as the electrophile in the substitution reaction, however no significant increase in yield was observed. All the alkynylic diols obtained showed good stability under light and air can be stored for months in a normal fridge with no degradation.

Kinetic resolution on analytical scale

The first step of studies towards the enzymatic kinetic resolution was conducted using **1a** as model substrate and vinyl acetate as acyl donor. In the literature it has been described that the polarity of anhydrous solvents can affect the enantioselectivity in some trans esterification reactions.[13] Therefore pure *n*-hexane and its mix with THF (50% v:v) were used as solvents. As can be seen in figure 2, the best result obtained for the resolution of **1a,** considering conversion and enantiomeric purity, employed 5 eq. of vinyl acetate in *n*-hexane:THF (50% v:v) for 4 hours. These conditions allowed for the resolution to afford both (*S*)-**8a** and (*R*)-**9a** in 99% of *e.e.*

A time point resolution study comparing solvents for the formation of (*S*)-**8a**, the first product of the resolution (light and dark blue lines, Figure 2), showed that in pure *n*-hexane the substrate (*R/S*)-**1a** was quantitatively converted to products in 15 minutes. Thus a fast and quantitative conversion of substrate into the mono-acetoxy product was observed. At the same period of time the consumption of (*R/S*)-**1a** by using *n*-hex:THF as solvent furnished the mono acylated (*S*)-**8a** in 89% *e.e*. These results show that the non-polar *n*-hexane makes the reaction faster (four times) even if in very few selectivity if compared with the use of *n*-hex:THF that takes one hour of reaction for total conversion of (*R/S*)-**1a** to (*S*)-**8a**. These interesting results concerning the enantioselective mono acylation of primary hydroxyl groups of substrates have not yet been thoroughly explored in this publication, as the focus was the formation of mono and bis-acetoxy products. For this, the total consumption of substrate was achieved using an excess of vinyl acetate. However, these observations open up potential new opportunities to explore the kinetic resolution with vinyl acetate as limiting agent.

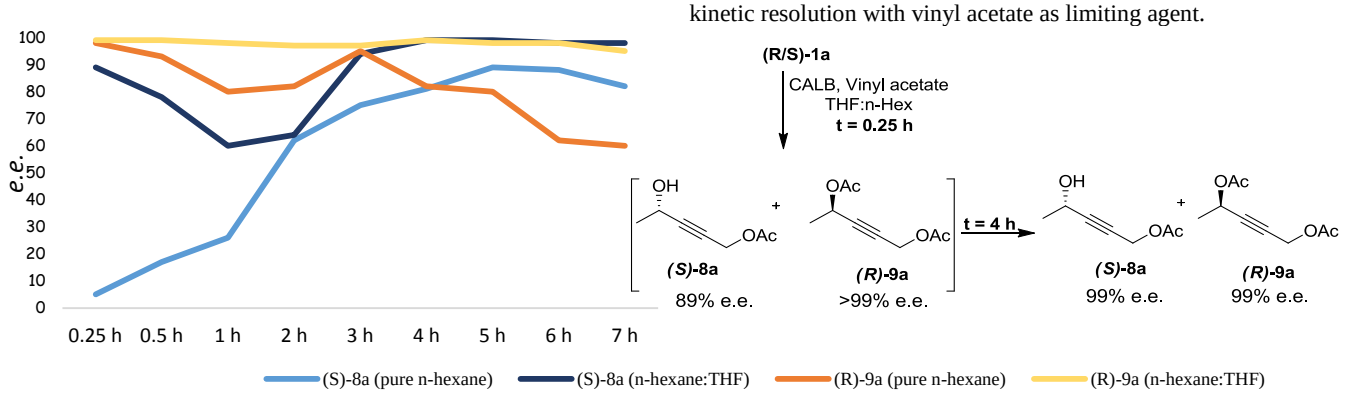


Fig. 2 Enzymatic kinetic resolution of **1a** - 100 mM solution of substrate in appropriate solvent (1mL), CALB (10 mg) and 500 mM solution of vinyl acetate at 35 ºC.

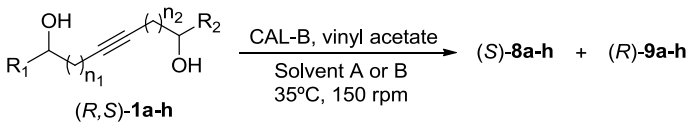
Journal Name RSCPublishing

ARTICLE

The absolute stereochemistry of (*S*)-(-)-**8a**, the less reactive enantiomer in the second round kinetic resolution, was assigned comparing the experimental optical rotation value $[\alpha]_D^{20}$ = -21.2 (*c* 1.0, $CHCl_3$), *e.e.* 99% with the literature, where $[\alpha]_D^{20}$ = +8.1 (*c* 0.71, $CHCl_3$), *e.e.* 90% is reported for (*R*)-(+)-**8a**.[14] With this, the resolution of (*R/S*)-**1a** has furnished both (*S*)-(-)-**8a** and (*R*)-(+)-**9a** in high *e.e.* (99%). The enantiopreference of CALB in the trans esterification of (*R*)-**8a** in the resolution is in agreement with Kazlauskas rule[15] considering methyl as small and the propargylic alcohol as large size groups respectively in the active site of the enzyme.

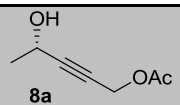
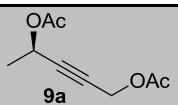
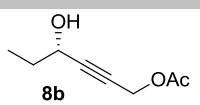
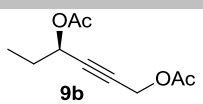
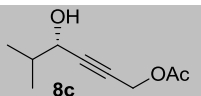
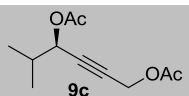
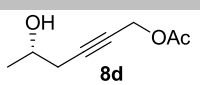
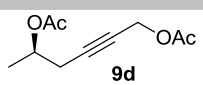
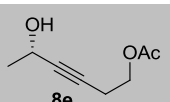
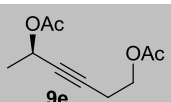
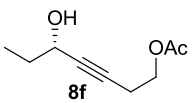
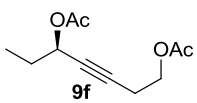
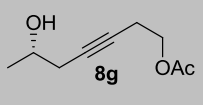
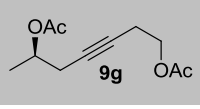
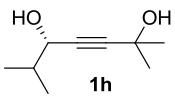
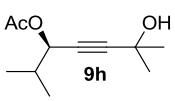
Kinetic resolution on preparative scale

After the initial promising results obtained for **1a**, the diols **1b-h** were subjected to EKR using both *n*-hexane and its mix with THF as solvents (Scheme 2). The best conditions after solvent screening for all substrates are summarised in table 1.



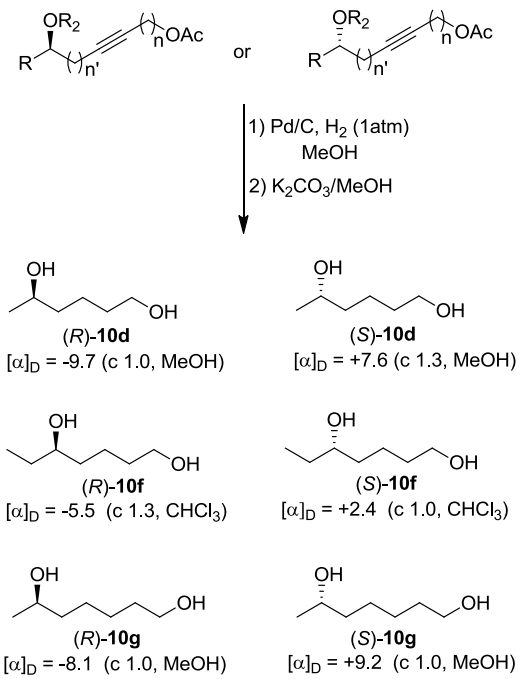
Scheme 2. Enzymatic kinetic resolution of diols **1a-h**.

Table 1. Enzymatic kinetic resolution of propargylic diols **1a-h** catalysed by CAL-B [Solvent A:*n*-hexane; Solvent B: *n*-hexane:THF(50%)].

Entry	Substrate	Products		Solvent	Yield (%)	t(h)	*e.e.*(%)	E
		First Round	Second Round					
1	1a	 **8a**	 **9a**	B	8a (44) 9a (47)	4	>99 99	>200
2	1b	 **8b**	 **9b**	A	8b (48) 9b (45)	2	95 99	>200
3	1c	 **8c**	 **9c**	A	8c (41) 9c (40)	48	96 94	>200
4	1d	 **8d**	 **9d**	B	8d (43) 9d (46)	0.5	>99 96	>200
5	1e	 **8e**	 **9e**	A	8e (40) 9e (44)	1	>99 99	>200
6	1f	 **8f**	 **9f**	A	8f (45) 9f (48)	1.5	85 99	>200
7	1g	 **8g**	 **9g**	A	8g (42) 9g (48)	0.75	>99 95	>200
8	1h	 **1h**	 **9h**	A	1h (48) 9h (44)	48	99 98	>200

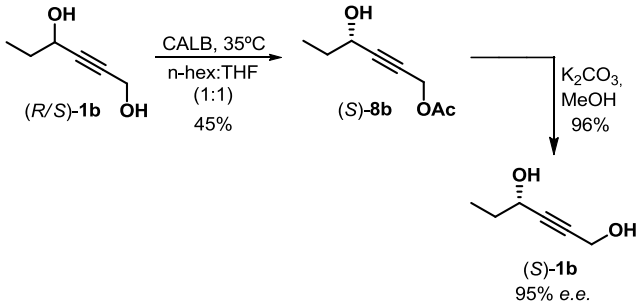
Subjecting all the diols to the two round sequence resolution, as can be observed in table 1, the best conditions for each substrate showed that different times and solvents were necessary. However, in all cases the first and the second products of resolution were obtained in their optically active form with high enantioselectivity values (E>200). The compounds **1a-b** and **1d-g** were resolved in less than four hours (Table 1, entries 1-2 and 4-7) while the diol **1c** which contains an isopropyl rather than methyl as medium size group, takes 48 hours to be totally converted (Table 1, entry 3). Surprisingly the kinetic products obtained from (*R/S*)-**1h** in the resolution were the nonreactive (*S*)-enantiomer of substrate and the mono acetoxy product **9h**, whereas the total acetylation reaction to furnish bis-acetoxy product was not observed. While **1c** and **1h** require 48 hours of reaction, no loss in the enantioselectivity was observed.

In order to determine the absolute configuration of all products provided from kinetic resolution with CAL-B, the assignments of the absolute stereochemistry were done comparing experimental specific rotation with literature data. For those compounds that have not been reported previously in the literature, the enantioenriched alkynylic substrates were chemically converted into the alkylic diols by a hydrogenation/hydrolysis sequence using Pd/C and K_2CO_3 in MeOH in two steps one pot operation. Thus, the stereochemistry of (*R*)-**9d**, (*S*)-**8f** and (*R*)-**9h** were indirectly assigned comparing the experimental optical rotation obtained with the literature (Scheme 3).



Scheme 3. Derivatization of alkynylic diols.

We were particularly interested in the preparation of (*S*)-**8b** in a large scale reaction since it could be directly used to synthesize significant amounts of chiral non-racemic (*S*)-Pent-2-yn-1,4-diol [(*S*)-**1b**], a natural product from *Clitocybe catinus*. Thus, after determining which isomer possess the desired (*S*)-configured enantiomer, the mono acetoxy (*S*)-**8b** (1.82g) was hydrolysed to furnish the compound (*S*)-**1b**, $[\alpha]_D$ = -7.2 (c 1.0, MeOH); $^{lit}[\alpha]_D$ = -5.2 (c 1.0, MeOH)[6] in 43% overall yield (Scheme 4).



Scheme 4. Route to (*S*)-**1b** from (R/S)-**1b**

Actually, the preparation of some functionalized alkynols containing compounds featuring biochemical relevance are under investigation. Thus a chemo enzymatic approach using the mentioned work could be combined with others synthetic strategies and applied for the synthesis of others target molecules. With that some chiral non-racemic poly-acetylene natural products should be prepared.

Conclusions

Several bis-substituted propargylic diols were prepared, some of them for the first time, in good isolated yields by adopting a strategy to minimize the use of protecting groups in the synthetic sequence.

The manly goal of this propose was the first EKR of internal alkynylic diols in a highly efficient enantioselectivity (E>200), and the application of this protocol on a short and large-scale synthesis of *(S)*-Pent-2-yn-1,4-diol [(*S*)-**1b**], a natural product from *Clitocybe catinus*. Actually, the synthesis of more challenging bioactive compounds by applying this strategy are currently in progress in our lab.

Acknowledgements

The authors thank UFPE, FACEPE, CAPES, CNPq and INCT-INAMI for Financial support and CETENE for the Infrastructure support.

Notes

[a]Departamento de Química Fundamental, Universidade Federal de Pernambuco - UFPE. Av. Jornalista Aníbal Fernandes S/N. Cidade Universitária, CEP: 50740-560, Recife-PE, Brasil. e-mail: princivalj@yahoo.com.br
[b]Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo-USP. Av. Prof. Lineu Prestes 748, Butantã, CEP: 05508-000, São Paulo-SP, Brasil.
†Electronic Supplementary Information (ESI) available: General procedure for chemical synthesis and Biocatalysis, and Spectral data for all propargylic substrates and products See DOI: 10.1039/b000000x/

References

[1](a) D. Listunov, V. Maraval, R. Chauvin and Y. Genisson, *Nat. Prod. Rep.* 2015, **32**, 49-75; (b) J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote and M. R. Prinsep *Nat. Prod. Rep.* 2003, **20**, 1-48; (c) J. C. Braekman, D. Daloze, C. Devijver, D. Dubut; R. W. M. van Soest, *J. Nat. Prod.* 2003, **66**, 871-872; (d) M. L. Lerch, M. K. Harper and D. J. Faulkner, *J. Nat. Prod.* 2003, **66**, 667-670; (e) J. Kobayashi, K. Naitohand K.Ishida, *J. Nat. Prod.* 1994, **57**, 1300-1303.

[2](a) B. W. Gung, D. T. Craft and J. Truelove, *Tetrahedron Asymmetry* 2007, **18**, 1284-1287; (b) S. Lopez, F. F. Trillo, P. Midon, L. Castedo and C. Saa, *J. Org. Chem.* 2005, **70**, 6346-6352; (c) B. W. Gung, H. Dickson and S. Shockley, *Tetrahedron Lett*. 2001, **42**, 4761-4763; (d) G. Zheng, W. Lu and J. Cai, *J. Nat. Prod.*1999, **62**, 626-628.
[3](a) A. Claesson, L.I. Olsson, *J. Am. Chem. Soc*. 1979, **101**, 7302-7311; (b) S. Ma, H. Hou, S. Zhao and G. Wang, *Synthesis*, 2002, **12**, 1643-1645; (c) J. Ye, W. Fan and S. Ma, *Chem. Eur. J.* 2013, **19**, 716-720.
[4]A.F. Thomas and H. Damn, *Tetrahedron Lett*. 1986, **27**, 505-506.
[5] T. R. Hoye, P. E. Humpal, J. I. Jimbez, M. J. Mayer, L. Tan and Z. Ye, *Tetrahedron Lett.*1994, **35**, 7517-7520.
[6] A. Arnone, G. Nasini and O. V. Pava, *Phytochemistry* 2000, **53**, 1087-1090.
[7] J. Shin, Y. Seo, K. W. Cho and J. R. Rho, *Tetrahedron* 1998, **54**, 8711-8720.
[8](a) K. Burgess and L. D. Jennings, *J. Am. Chem. Soc*. 1991, **113**, 6129-6139; (b) B. Morgan, A. C. Oehlschlager and T. M. Stokes, *J. Org. Chem.* 1992, **57**, 3231-3236; (c) M. Kurihara, K. lshii, Y. Kasahara and N. Miyata, *Tetrahedron Letters*, 1999, **40**, 3183-3184.
[9] (a) C. Raminelli, J. V. Comasseto, L. H. Andrade and A. L. M. Porto, *Tetrahedron: Asymmetry*, 2004, **15**, 3117-3122; (b) D. Xu, Z. Li and S. Ma, *Tetrahedron Letters*, 2003, **44**, 6343-6346; (c) P. Chen, X. Zhu, *J. Mol. Catal. B: Enzym.* 2013, **97**, 184-188.
[10](a) T. Schubert, W. Hummel, M. R. Kula and M. Müller, *Eur. J. Org. Chem.* 2001,4181-4187; (b) C. W. Bradshaw, W. Hummel and C. H. Wong, *J. Org. Chem.* 1992, **57**, 1532-1536.
[11] (a) S. Hu, L. P. Hager, *J. Am. Chem. Soc.* 1999, **121**, 872-873; (b) Y. Chen, F. Lie and Z. Li, *Adv. Synth. Catal.* 2009, **351**, 2107-2112.
[12] C.G. Nasveschuk, J. D. Frein, N. T. Jui and T.Rovis, *Org. Lett*. 2007, **9**, 5099-5102.
[13](a) P. A. Fitzpatrick and A. M. Klibanov, *J. Am. Chem. Soc.* 1991, **113**, 3166-3171; (b) K. Nakamura, M. Kinoshita and A. Ohno, *Tetrahedron* 1995, **51**, 8799-8808.
[14] Barry M. Trost and Adrien Quintard, *Angew. Chem. Int. Ed*. 2012, **51**, 6704-6708.
[15]R. J. Kazlauskas, A. N. E. Weissfloch, A. T. Rappaport and A. Cuccia, *J. Org. Chem.* 1991, **56**, 2656-2665.
[16]X.-W. Chang, D.-W. Zhang, F. Chen, Z.-M. Dong and D. Yang, *Synlett* 2009, 3159-3162.
[17] S. Hu and L. P. Hager, *J. Am. Chem. Soc.* 1999**, 121**, 872-873.
[18] S. Harada, R. Takita, T. Ohshima, S. Matsunaga and M. Shibasaki, *Chem. Commun.*, 2007, **9**, 948-950.
[19] K. Wada and T. Ishida, *J. Chem. Soc., Perkin Trans. I*, 1979, 1154-1158.
[20] K. Seehafer, F. Rominger, G. Helmchen, M. Langhans, D. G. Robinson, B. Ozatä, B. Brügger, J. R. P. M. Strating, F. J. M. van Kuppeveld and C. D. Klein, *J. Med. Chem.* 2013, **56**, 5872-5884.
[21] K. Edegger, W. Stampfer, B. Seisser, K. Faber, S. F. Mayer, R. Oehrlein, A. Hafner and W. Kroutil, *Eur. J. Org. Chem.* 2006, 1904-1906.
[22] C. –S. Chen, Y. Fujimoto, G. Girdaukas, C. J. Sih *J. Am. Chem. Soc.* 1982, **104**, 7294–7299.