# ChemComm

## Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. V. Barysevich, V. V. Kazlova, A. G. Kukel, A. I. Liubina, A. L. Hurski, V. N. Zhabinskii and V. A. Khripach, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC00888D.


This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC00888D

Journal Name

COMMUNICATION

# Stereoselective synthesis of α-methyl and α-alkyl ketones from esters and alkenes via cyclopropanol intermediates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

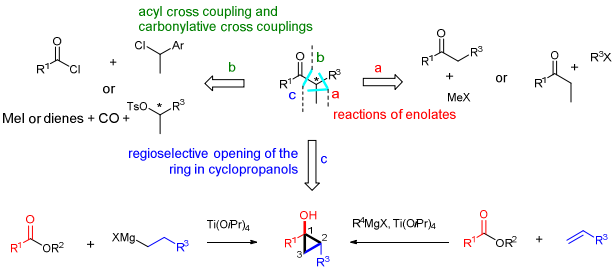
www.rsc.org/

Maryia V. Barysevich,[a] Volha V. Kazlova,[a] Aliaksandr G. Kukel,[a] Aliaksandra I. Liubina,[a] Alaksiej L. Hurski,*[a] Vladimir N. Zhabinskii[a] and Vladimir A. Khripach[a]

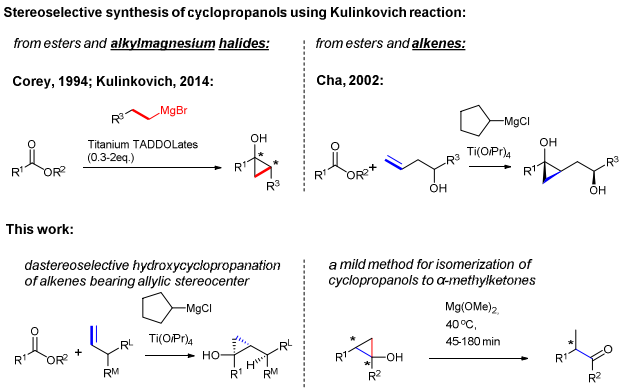
**Alkenes bearing a stereocenter in allylic position were found to undergo Kulinkovich hydroxycyclopropanation with good diastereoselectivity. For the isomerization of the resulting cyclopropanols to diastereomerically enriched α-methyl ketones, a new mild regioselective method has been developed. A sequence of stereoselective cyclopropanation and cyclopropanol ring opening was successfully employed for the construction of the C20 stereocenter in steroids.**

Chiral α-methyl substituted ketone units are widely abundant in natural products and numerous methods have been developed for their asymmetric synthesis (Scheme 1). The most common approaches are based on auxiliary- or catalyst-controlled reactions of enolates (pathway a).[1] An alternative disconnection strategy was utilized in the synthesis of the unit *via* reductive acyl cross-coupling,[2] carbonylative cross-coupling[3] (pathway b) and through Kulinkovich cyclopropanation[4] followed by the cyclopropanol ring opening (pathway c).[5] The latter approach remains underdeveloped but its implementation in synthesis would allow to trace the chiral α-methylketones back to esters and terminal olefins, which are stable and readily accessible starting materials. Coupling of functionalized esters with alkenes into advanced cyclopropanol intermediates has been successfully used in the synthesis of natural compounds[4b,6] but in all these reports the three-carbon rings were further transformed to achiral or racemic fragments. For successful employment of the cyclopropanation strategy in the synthesis of chiral α-methylketones, both efficient asymmetric modification of Kulinkovich reaction and a reliable procedure for the ring opening of stereoisomerically enriched cyclopropanols are required.

To date, significant progress has been achieved in the development of the asymmetric Kulinkovich hydroxycyclopropanation (Scheme 2). Twenty years after the first report on enantioselective synthesis of 1(*S*)-methyl-2(*R*)-phenylcyclopropanol in 1994 by Corey,[7] Kulinkovich[8] disclosed a general catalyst-controlled protocol for the reaction of esters with alkylmagnesium halides. However, intermolecular stereoselective hydroxycyclopropanation of alkenes with esters is less developed and limited to a substrate-controlled reaction of secondary homoallylic alcohols reported by Cha.[9]




**Scheme 1.** Strategies toward stereoselective synthesis of α-methyl ketones.




**Scheme 2.** Asymmetric Kulinkovich cyclopropanation and isomerization of cyclopropanols to α-methyl ketones

Numerous regioselective methods for opening the ring in 1,2-disubstituted cyclopropanols have been discovered.[4b,5] Reactions with bases or electrophiles usually lead to the cleavage of C1-C3 bond, while reactions proceeding *via* radical mechanism result in breaking of the C1-C2 bond.[5] However, preparation of chiral α-methyl ketones from cyclopropanols is still a challenging task. The isomerization may proceed with low regioselectivity[5a,8a] and the α-stereocenter in ketones is

[a] *Laboratory of Steroids, Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich 5/2, 220141 Minsk, Belarus, Email: AHurski@iboch.by*

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

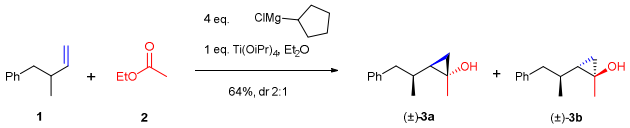
View Article Online
DOI: 10.1039/C8CC00888D




prone to racemization. Only organozinc reagents[10] and tartaric acid on alumina[8a] have been reported to promote this transformation but the scope of these methods is narrow.

In this communication, we report a new group of alkenes that undergoes Kulinkovich hydroxycyclopropanation with good diastereoselectivity and a new mild method for regioselective isomerization of chiral cyclopropanols to α-methyl ketones.

We started the investigation with the preparation of stereoisomerically enriched cyclopropanols. Our efforts were directed toward their synthesis from alkenes, which are more readily available and stable than Grignard reagents. We speculated that alkenes bearing a stereocenter adjacent to double bond might be hydroxycyclopropanated diastereoselectively.[11] To test this assumption, substrate **1** was reacted with ethyl acetate (**2**) and a 2:1 mixture of diastereomeric cyclopropanols (±)-**3** was obtained (Scheme 3). With this promising result, we further examined the substrate **4a** (Table 1) in which the steric volumes of allylic substituents differ stronger than those in alkene **1**. The resulting cyclopropanol **5a** was obtained in a 76% yield and with a good 6:1 diastereoselectivity.[12, 13]

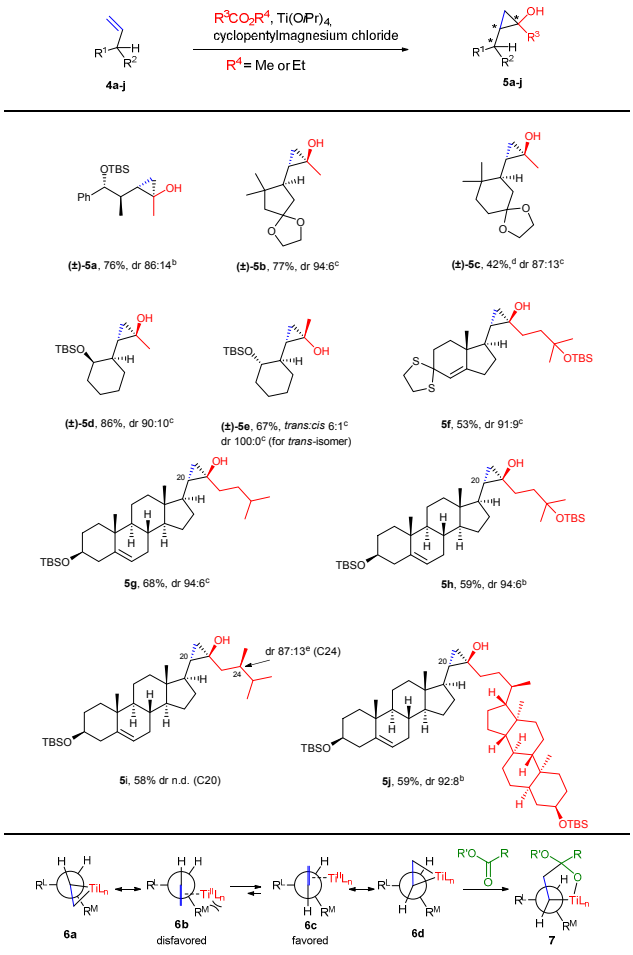



**Scheme 3**. Diastereoselective Kulinkovich reaction of alkene **1** with ethyl acetate (**2**).

Next, we explored the scope of the diastereoselective cyclopropanation and the results are summarized in Table 1. The reactions were carried out in THF for substrates with dioxolane and dithiolane groups or in ether for other substrates. Hydroxycyclopropanation of all tested alkenes proceeded at the same diastereotopic face of the double bond and in most cases *cis*-1,2-dialkylcyclopropanols were formed. Cyclopropanols (±)-**5b**, (±)-**5d-e** and **5f-j** were obtained with up to 94:6 diastereoselectivity and in good yields. Only alkene **4c** was significantly less reactive. A satisfactory 42% yield of (±)-**5c** was achieved using an excess of ester, catalyst and Grignard reagent. Surprisingly, cyclopropanol (±)-**5e** was formed preferentially as a *trans*-1,2-dialkyl isomer. High *trans*-selectivity is typical for the hydroxycyclopropanation of homoallylic alcohols because of the coordination of catalyst with a hydroxyl group.[9] It is likely that silyloxy group in **4e** assists formation of *trans*-(±)-**5e** through the coordination with the titanium center. Then our attention was turned to easily available bi- and tetracyclic substrates **4f** and **4g**[14] since their diastereoselective hydroxycyclopropanation could be used in synthesis of steroids. To our delight, **4f** and **4g** underwent smooth reaction with appropriate ester partners to furnish cyclopropanols **5f-i**. Diastereomeric purity at the created C20 stereocenter in the obtained steroidal cyclopropanols was good including the product **5i**.[15] Coupling of the steroidal alkene **4g** with similar in size ester also proceeded successfully providing cyclopropanol **5j** without a significant drop in yield or stereoselectivity.

The observed diastereoselectivity may be explained by the preferential formation of the intermediate Ti(II)-alkene complex **6c/6d** in which repulsive interactions between the substrate and titanium ligands are minimized in contrast to the disfavored complex **6b/6a**. In addition, insertion of ester carbonyl group into C-Ti bond of titanacyclopropane **6d** to form **7** might proceed faster than the insertion into **6a** because of steric considerations.

**Table 1.** Scope for the diastereoselective synthesis of cyclopropanols **5**.[a]




[a]Reaction conditions: alkene (1 equiv.), ester (2 equiv. of EtOAc, 1 equiv. of other esters), $Ti(OiPr)_4$ (1 equiv.), cyclopentylmagnesium chloride (4 equiv.), THF (0.05 M, synthesis of (±)-**5b-c**, **5f**) or ether (0.05 M, synthesis of (±)-**5a**, (±)-**5d-e**, **5g-j**) at 0 °C ((±)-**5a**, (±)-**5d-e**, **5g-h**, **5i**) or at rt ((±)-**5b-c**, **5f**, **5i**). [b]dr of α-methylketones obtained by isomerization of crude cyclopropanols. [c]Determined from $^1H$ NMR spectra of crude cyclopropanol. [d]4 equiv. of EtOAc, 2 equiv. of $Ti(OiPr)_4$ and 8 equiv. of cyclopentylMgCl were used. [e]er of the ester precursor.

With the synthesized cyclopropanols in our hands, we started investigations toward the development of the procedure for their isomerization to α-methyl ketones. Disappointingly, both of known approaches failed to provide smooth ring opening of cyclopropanol **5g**. Treatment of the latter compound with $EtZnCH_2I$[10] led to a complex mixture while the reaction with tartaric acid on alumina[8a] proceeded with unsatisfactory regioselectivity and was accompanied by desilylation. After experimentation with salts and oxides (for details, see SI), we

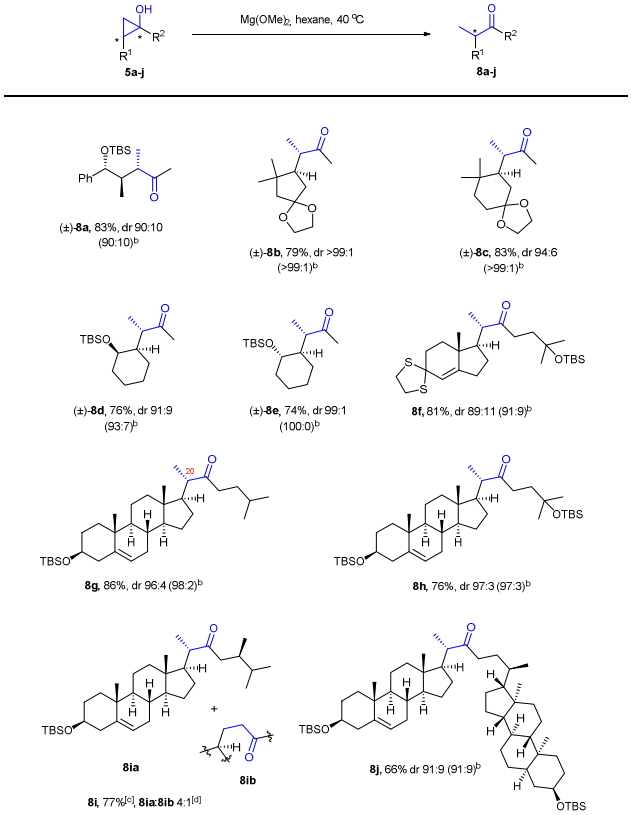
View Article Online
DOI: 10.1039/C8CC00888D





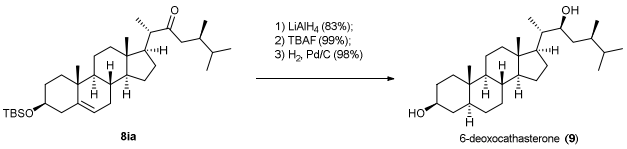
found that the transformation of **5g** to α-methyl ketone **8g** proceeds smoothly in the presence of the excess of magnesium methylate at 40 °C within 45 min. The best results were obtained in hexane, although other solvents could be used as well (for details, see SI). Only very little epimerization was observed under the reaction conditions (see Table 2). Cyclopropanols **5** were successfully isomerized providing the desired ketones **8** in good yields with excellent regioselectivity and high diastereomeric purity. The only exception was cyclopropanol **5i**. Its isomerization proceeded more slowly (3 h) and less regioselectively affording a 4:1 mixture of **8ia** and its isomer **8ib**. This mixture was chromatographically inseparable but its recrystallization from methanol provided the pure α-methyl ketone **8ia**. Low regioselectivity in the isomerization of **5i** could be explained by increased steric hindrance around its cyclopropanol unit. Presence of the methyl branch at C24 may disfavour the proper coordination of $Mg(OMe)_2$ with the hydroxyl group.

**Table 2.** Scope for the $Mg(OMe)_2$-mediated isomerization of cyclopropanols **5** to α-methyl ketones **8**.[a]



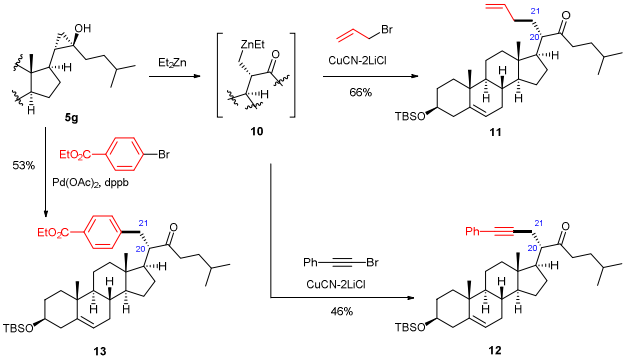

[a]Reaction conditions: $Mg(OMe)_2$ (10 fold w/w excess), hexane (5% w/w solution of **5**), 40 °C, 45 min; diastereomeric ketones are inseparable by column chromatography, dr of the products was determined from $^1$H NMR spectra of crude **8**. [b]dr of the starting cyclopropanols **5**. [c]Reaction time: 3 h. [d]After recrystallization from MeOH, pure **8ia** was obtained.

The investigated sequence of diastereoselective Kulinkovich hydroxycyclopropanation of alkene **4g** and isomerization of the resulting cyclopropanols offers a novel way for the synthesis of steroidal side chains with the natural configuration at C20.[16] Compounds **8f-i** belonging to cholestane, 25-hydroxycholestane or campestane series were synthesized from alkenes **4f** or **4g** and readily available appropriate esters (see SI). To confirm the configuration at C20, ketone **8ia** was transformed to the known phytosterol 6-deoxocathasterone (**9**),[17] an intermediate in the biosynthesis of plant growth hormone brassinolide (Scheme 4).[18] Spectra of **9** were identical to those reported in the literature.[19]




**Scheme 4**. Synthesis of 6-deoxocathasterone (**9**).

After successful application of cyclopropanols **5f-j** in the synthesis of steroids with natural side chains, we assumed that their metal-catalyzed cross-coupling reactions[5b,20] could be suitable for construction of homoallyl-, propargyl- or benzyl-substituted at C20 steroids. Replacement of the natural methyl group at C20 with bulkier substituents was successfully applied to decrease undesired side effects of vitamin D derivatives possessing anti-cancer activity.[21] Ring opening of **5g** with $Et_2Zn$ followed by allylation[22] or alkynylation[23] of the intermediate homoenolate **10** led to steroids **11** and **12** bearing the modified at C20 side chains. Palladium-catalyzed arylation[24] of **5g** also proceeded smoothly furnishing arylated steroid **13** (Scheme 5).




**Scheme 5**. Synthesis of the 21-substituted steroids **11-13**.

In conclusion, we have developed a convenient protocol for the transformation of stereoisomerically enriched cyclopropanols to α-methyl ketones. We have also established that alkenes bearing a stereocenter at the allylic carbon undergo Kulinkovich hydroxycyclopropanation with a good level of diastereoselectivity. The developed transformation has been applied for the attachment of side chains to the steroidal nucleus. In addition, a synthesized steroidal cyclopropanol was successfully tested in the ring opening cross-coupling reactions providing corresponding α-alkyl ketones.

We thank Belarusian Foundation for Fundamental Research (project X17PM-039) and Russian Science Foundation (№ 16-16-04057, preparation of steroids **8g-i**) for the financial support. We thank Dr. A. Baranovsky for assistance with NMR

View Article Online
DOI: 10.1039/C8CC00888D


spectroscopy, Dr. A. Yantsevich, M. Trawkina and Dr. Y. Kozyrkov for HRMS analysis, T. Shkel for MALDI MS analysis, Dr. V. Gromak for IR spectra.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

1 (*a*) E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*, Wiley, 2009; (*b*) M. Braun, *Modern Enolate Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, 2015; (*c*) R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.*, 2017, **56**, 9278-9209.

2 A. H. Cherney, N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.,* 2013, **135**, 7442-7445.

3 (*a*) B. T. Sargent, E. J. Alexanian, *J. Am. Chem. Soc.,* 2017, **139**, 12438-12440; (*b*) J. P. Collman, R. G. Finke, J. N. Cawse, J. I. Brauman, *J. Am. Chem. Soc.,* 1977, **99**, 2515-2526.

4 (*a*) J. K. Cha, O. G. Kulinkovich, *Org. React.*, 2012, **77**, 3-159; (*b*) O. G. Kulinkovich, *Cyclopropanes in Organic Synthesis*, John Wiley & Sons, Inc, 2015.

5 For reviews on reactions of cyclopropanols, see: (*a*) O. G. Kulinkovich, *Chem. Rev.,* 2003, **103**, 2597-2632; (*b*) A. Nikolaev, A. Orellana, *Synthesis*, 2016, **48**, 1741-1768; for recent examples on ring opening of 1,2-disubstituted cyclopropanols, see: (*c*) H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.,* 2015, **137**, 3490-3493; (*d*) C. Zhu, X. Fan, H. Zhao, J. Yu and X. Bao, *Org. Chem. Front.,* 2016, **3**, 227-232; (*e*) N. Tumma, E. Gyanchander, J. K. Cha, *J. Org. Chem.*, 2017, **82** , 4379–4385; (*f*) Y. A. Konik, M. Kudrjashova, N. Konrad, S. Kaabel, I. Järving, M. Lopp, D. G. Kananovich, *Org. Biomol. Chem.*, 2017, **15**, 4635-4643; (*g*) Ł. Woźniak, G. Magagnano, P. Melchiorre, *Angew. Chem. Int. Ed.,* 2018, **57**, 1068–1072; (*h*) A. Nikolaev, C. Y. Legault, M. Zhang, A. Orellana, *Org. Lett.*, 2018, **20**, 796−799; (*i*) I. Novikau, A. Hurski, *Tetrahedron,* 2018, **74**, 1078-1084.

6 For review, see: (*a*) I. Haym, M. A. Brimble, *Org. Biomol. Chem.*, 2012, **10**, 7649-7665; for application of the Kulinkovich reaction in the synthesis of natural compounds for convergent coupling of functionalized subunits, see: (*b*) K. A. Keaton, A. J. Phillips, *Org. Lett.*, 2007, **9**, 2717-2719; (*c*) K. A. Keaton, A. J. Phillips, *Org. Lett.*, 2008, **10**, 1083-1086; (*d*) A. L. Hurski, O. G. Kulinkovich, *Tetrahedron Lett.*, 2010, **51**, 3497-3500; (*e*) A. L. Hurski, O. G. Kulinkovich, *Russ. J. Org. Chem.*, 2011, **47**, 1653-1674; (*f*) J. McCabe, A. J. Phillips, *Tetrahedron*, 2013, **69**, 5710-5714.

7 E. J. Corey, S. A. Rao, M. C. Noe, *J. Am. Chem. Soc.,* 1994, **116**, 9345-9346.

8 (*a*) Y. A. Konik, D. G. Kananovich, O. G. Kulinkovich, *Tetrahedron*, 2013, **69**, 6673-6678; (*b*) O. G. Kulinkovich, D. G. Kananovich, M. Lopp, V. Snieckus, *Adv. Synth. Catal.,* 2014, **356**, 3615-3626.

9 L. G. Quan, S.-H. Kim, J. C. Lee, J. K. Cha, *Angew. Chem. Int. Ed.*, 2002, **41**, 2160-2162.

10 P. P. Das, B. B. Parida, J. K. Cha, *Arkivoc*, 2012, 74-84.

11 Hydroxycyclopropanation of alkenes bearing a methyl branch at the allylic carbon has been reported previously but diastereoselectivity of the reaction was not noted: (*a*) S.-G. Li, Y. Wu, *Chem. Asian J.*, 2013, **8**, 2792-2800; (*b*) W.-B. Han, S.-G. Li, X.-W. Lu, Y. Wu, *Eur. J. Org. Chem.* 2014, **2014**, 3841-3846. See also Ref.[6c,f]

12 Diastereomeric cyclopropanols **5** have very close Rf values and for most of the products only partial separation of isomers is possible by column chromatography on silica gel. Complete preparative separation of the major isomers was performed only for the products (±)-**5b-c**. dr of cyclopropanols (±)-**5b-e, 5f,g** was determined from $^{1}$H NMR spectra but for cyclopropanols (±)-**5a, 5h,j**, direct determination of dr was not possible. To evaluate their diastereomeric purity, crude cyclopropanols were transformed to α-methyl ketones (±)-**8a, 8h,j**. Their dr were easily obtained from $^{1}$H NMR spectra (see SI).

13 Relative configuration of the synthesized cyclopropanols was determined after their transformation to α-methyl ketones by considering coupling constants and 2D NOESY NMR spectra or by transformation to known compounds (see SI).

14 For the synthesis of **4g** from commercial pregnenolone acetate, see: R. D. Dawe, J. L. C. Wright, *Can. J. Chem.*, 1987, **65**, 666-669.

15 dr of **5i** was not determined precisely as the analysis was complicated by the presence of the additional impure C24 stereocenter.

16 Attachment of side chains to steroidal cores is a laborious task. For a review see: B. B. Shingate, B. G. Hazra, *Chem. Rev.*, 2014, **114**, 6349-6382.

17 C. Yong-Hwa, S. Fujioka, T. Nomura, A. Harada, T. Yokota, S. Takatsuto, A. Sakurai, *Phytochemistry*, 1997, **44**, 609-613.

18 V. A. Khripach, V. N. Zhabinskii, A. E. de Groot, *Brassinosteroids: A New Class of Plant Hormones*, Academic Press, San Diego, 1999.

19 *(a)* S. Takatsuto, H. Kuriyama, T. Noguchi, H. Suganuma, S. Fujioka, A. Sakurai, *J. Chem. Res., Synop.*, 1997, 418-419; *(b)* A. L. Hurski, V. N. Zhabinskii, V. A. Khripach, *Steroids*, 2012, **77**, 780-790.

20 *(a)* D. Rosa, A. Nikolaev, N. Nithiy, A. Orellana, *Synlett*, 2015, **26**, 441-448; *(b)* G. Fumagalli, S. Stanton, J. F. Bower, *Chem. Rev.,* 2017, **117**, 9404-9432.

21 P. Gonzalo, L. R. Marcos, P.-G. Xenxo, G. Zoila, P. Manuel, *Curr. Top. Med. Chem.*, 2014, **14**, 2388-2397.

22 P. P. Das, K. Belmore, J. K. Cha, *Angew. Chem. Int. Ed.*, 2012, **51**, 9517-9520.

23 R. V. N. S. Murali, N. N. Rao, J. K. Cha, *Org. Lett.*, 2015, **17**, 3854-3856.

24 D. Rosa, A. Orellana, *Chem. Commun.*, 2013, **49**, 5420-5422.

View Article Online
DOI: 10.1039/C8CC00888D

Diastereoselective Kulinkovich hydroxycyclopropanation of alkenes with esters and a protocol for isomerization of chiral cyclopropanols to α-methyl ketones have been developed.