

BENZYLIC OXO-FUNCTIONALISATION OF INDANE DERIVATIVE BY BENZYLIC BROMINATION FOLLOWED BY KORNBLUM-TYPE OXIDATION

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1,1'-Dimethoxy-1,1'-diphenyl-2,2'-spirobiindane and indane, as a model compound, were treated with various oxidising agents in order to achieve benzylic oxo-functionalisation. The model compound, indane, was successfully converted directly to 1-indanone, using several benzylic oxidation procedures, but when they were used on the 1,1'-dimethoxy-1,1'-diphenyl-2,2'-spirobiindane derivative, they either failed, led to fragmentation or complex mixture of products was obtained. The benzylic oxo-functionalisation was achieved on the 1,1'-dimethoxy derivative in two steps using benzylic bromination/silver-assisted Kornblum type oxidation. The observed reactivity of these systems can be rationalised by steric hindrance arguments and the ring opening tendencies of the 1,1'-disubstituted-1,1'-diphenyl-2,2'-spirobiindane derivatives.

Keywords: benzylic oxidation, benzylic bromination, the Kornblum reaction, indane derivative.

AIMS AND BACKGROUND

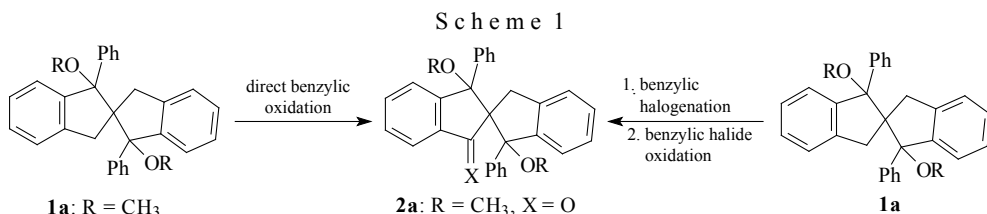
Oxidation reactions and reagents are of enormous importance in organic chemistry both in research laboratories and industry^{1,2}. One of the many possible transformations is the oxidation of organic substrates containing benzylic hydrogens. Especially appealing is the transformation of benzylic CH₂ group to a ketone (Ar-CH₂-R' to Ar-C=O (R')). The benzylic oxidation of alkyl aromatics provides carbonyl compounds which are quite useful from synthetic point of view. There are two main approaches usually employed for this transformation: direct oxidation and two-step oxidation (benzylic halogenations/oxidation).

Many methodologies have been developed for the direct benzylic oxidation. Traditionally, this transformation has been carried out using a stoichiometric amount

of metal-based reagents, usually heavy metal such as chromium(VI) or manganese^{1,3}. Another more recent approach is to use only catalytic amount of heavy metal in combination with excess amount of oxidant (H₂O₂, *tert*-butyl hydroperoxide, etc.)⁴. Nowadays the preferred methods of oxidation use metal-free reagents in stoichiometric amounts, such as hypervalent iodine reagents⁵, dimethyl dioxirane^{6,7}-type reagents among others. The new wave of green chemistry has been focused on developing effective metal-free methodologies using molecular oxygen⁸.

It is well-known that the outcome, yield and the selectivity of benzylic oxidation reactions depend on the structure of alkylarene (electron density at the benzylic position and steric factors among others). As a part of mechanistic study involving 2,2'-spirobiindane systems, the goal was to prepare several derivatives based on the 1,1'-disubstituted-2,2'-spirobiindan-1-one and 1,1'-disubstituted-2,2'-spirobiindan-1,1'-dione systems. The attention was focused on 1,3'-dimethoxy-1,3'-diphenyl-2,2'-spirobiindan-1-one (**2a**) as the initial synthetic target (Scheme 1).

The idea was to prepare 1,1'-dimethoxy-1,1'-diphenyl-2,2'-spirobiindane, **1a** (known in literature⁹) and then to subject it to direct benzylic oxidation to obtain **2a**. The **1a** has two indane units connected in a spirocyclic fashion. Depending on the structure of the substrate, sometimes it is not possible to achieve direct benzylic oxidation. In such cases, benzylic halogenation (most frequently bromination) is carried out, and the corresponding benzylic halide is oxidised to the desired benzylic carbonyl compound (Scheme 1).



Herein the results of the efforts to monofunctionalise the benzylic position of 1,1'-dimethoxy-1,1'-diphenyl-2,2'-spirobiindane derivatives are presented.

EXPERIMENTAL

GENERAL

2,2'-Azobis(2-methylpropionitrile) (AIBN), dimethyl sulphoxide (anhydrous, 99.9%, Sure seal™), carbon tetrachloride, dichloromethane and silver tosylate were obtained from Sigma-Aldrich. Triethylamine, sodium sulphate and magnesium sulphate were obtained from Merck. N-bromosuccinimide (Sigma-Aldrich) was recrystallised from water and dried *in vacuo*. Melting points were determined using a Thomas-Hoover apparatus and were uncorrected. NMR spectra were recorded on a Bruker 400 MHz

instrument using deuterated benzene (C_6D_6) as solvent. The IR spectrum was recorded on a Varian Excalibur 3100 Series FT-IR spectrometer using KBr pellet method. The number of hydrogens on each carbon was determined from ^{13}C NMR and $^{135}DEPT$ spectra. Atmospheric pressure chemical ionization (APCI-MS) mass spectra were generated using a Quattro II mass spectrometer (Micromass, Beverly, MA) using a corona needle potential of 4000 V and probe temperature of 400°C. The samples were delivered using a 0.5 ml/min flow of methanol/dichloromethane (50:50 v/v). Thin layer chromatography (TLC) was carried out using Merck pre-coated plates (60 F₂₅₄, 250 μ m) and preparative flash chromatography¹⁰ was performed using Merck silica gel 60 (230–400 mesh).

SYNTHESIS

1,1'-Dimethoxy-1,1'-diphenyl-2,2'-spirobiindane (**1a**) was prepared using literature procedure⁹.

1,3'-Dimethoxy-1,3'-diphenyl-2,2'-spirobiindan-1-one (**2a**):

A mixture of **1a** (0.600 g, 1.389 mmol), *N*-bromosuccinimide (0.616 g, 3.465 mmol), 2,2'-azobis(2-methylpropionitrile) AIBN (0.020 g) and carbon tetrachloride was refluxed for 4 h. The orange red reaction mixture was cooled to room temperature and diluted with dichloromethane (40 ml). The combined organic phase was washed with saturated sodium bicarbonate (2 \times 20 ml) and water (3 \times 20 ml). Drying over sodium sulphate and gentle evaporation of the solvent (< 35°C) gave yellow powder, which was dried *in vacuo* overnight. The crude solid was subjected to bromination using the same quantities of NBS and AIBN and carbon tetrachloride as mentioned above and the mixture was refluxed for 4 h. This protocol was repeated one more time. Prolonged reflux times (> 6 h) lead to decomposition both of **1a** and the monobromo product. The final yellow solid contained some unreacted starting material and the desired 3-bromo-1,1'-dimethoxy-1,1'-diphenyl-2,2'-spirobiindane (~70%); 1H NMR (400 MHz, C_6D_6): 8.42–6.70 (m, 18 H), 5.62 (s, 1 H), 3.48 (d, *J* = 15.5 Hz, 1 H), 2.63 (s, 3 H), 2.55 (s, 3 H). The crude mixture was dissolved in anhydrous dimethyl sulphoxide (15 ml) and silver tosylate (0.500 g, 1.79 mmol) was added, followed by triethylamine (1.5 ml, 1.089 g, 10.8 mmol). The flask was immediately lowered into an oil bath pre-heated at 45°C and covered with aluminum foil. The reaction mixture turned progressively darker to become dark brown at the end. After 9 h at 45°C and 19 h at room temperature it was diluted with dichloromethane (50 ml) and filtered through a pad of magnesium sulphate (to remove the silver bromide). The filter cake was washed with additional dichloromethane (100 ml) and hexane (15 ml), and the combined organic solvents were washed with water (200 ml). The water layer was back-washed with dichloromethane (2 \times 25 ml). The combined organic layers were washed with water (2 \times 150 ml) and dried over sodium sulphate. Removal of solvent gave 0.548 g of brown fluffy solid, which was subjected to flash column chromatography, eluting with 45% dichloromethane in hexanes. The desired product (**2a**) was obtained as a light yellow solid, 0.158 g (28%). m.p. 110–112°C.

1,3'-Dimethoxy-1,3'-diphenyl-2,2'-spirobiindan-1-one (**2a**):

¹H NMR (400 MHz, C₆D₆): 8.20 (d, J = 7.55 Hz, 1 H), 7.70–6.84 (m, 17 H), 3.19 (d, J = 15.3 Hz, 1 H), 2.72 (s, 3 H), 2.63 (s, 3 H), 2.45 (d, J = 15.3 Hz, 1 H), 2.84 (m, 2 H), 2.36 (s, 3 H);

¹³C NMR (100 MHz, C₆D₆): 202.77 (C=O), 151.41 (C), 144.21 (C), 142.83 (C), 138.88 (C), 138.74 (C), 136.98 (C), 133.09 (CH), 132.79 (CH), 131.46 (CH), 129.85 (CH), 128.74 (CH), 128.41 (CH), 128.08 (CH), 127.86 (CH), 127.44 (CH), 127.42 (CH), 126.84 (CH), 125.93 (CH), 125.58 (CH), 125.31 (CH), 95.22 (C), 92.43 (C), 76.80 (C, spiro), 51.74 (CH₃), 50.33 (CH₃), 42.07 (CH₂);

IR (KBr): 3055 (w), 3025 (w), 2934 (m), 2822 (m), 1720 (s, C=O), 1604 (m), 1481 (m), 1471 (m), 1460 (m), 1446 (s), 1291 (s), 1085 (s), 1054 (s), 1030 (m), 765 (s), 740 (s), 706 (s);

Calcd. for C₃₁H₂₈O₂: C 86.08%, H 6.52%. Found: C 86.18%, H 6.44%.

APCI-MS (*m/z*, rel. intensity): 417 (6%), 416 (31%), 415 (MH⁺-CH₃OH, 100%).

RESULTS AND DISCUSSION

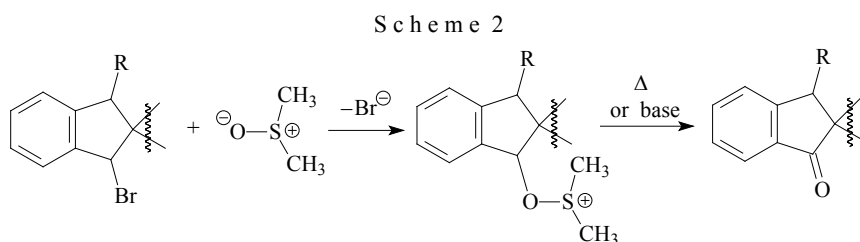
Because the outcome of the benzylic oxidation depends on the structure of the alkylarene, indane was selected as the model substrate. Indane was used as a model compound to see if the oxidising agent and the literature procedures were suitable for benzylic oxidation (based on the yield of indan-1-one). The oxidation reactions of indan-1-one and 1,1'-dimethoxy-1,1'-diphenyl-2,2'-spirobiindane (**1a**) were monitored by TLC, gas chromatography and/or ¹H NMR spectroscopy. After a literature survey of suitable reagents for benzylic oxidation the standard oxidising agents based on manganese and chromium were tried. The 'classical' oxidation using potassium permanganate was too harsh and led to the destruction of the spirocyclic system of **1a**. The several protocols using various chromium(VI) based reagents that were effective for the benzylic oxidation of the model compound (Harms et al.¹¹, Jacobsen¹², (CrO₃, AcOH), Rathore et al.¹³ (PCC)) were not suitable for the oxidation of **1a**. Most of them gave a complex mixture of the desired product and ring-opened oxidised by-products. With other milder, metal-free reagents and protocols that were successful for benzylic oxidation of indane, such as 2-iodoxybenzoic acid (IBX) used by Nicolau and co-workers¹⁴, dimethyldioxirane used by Kuck and Schuster¹⁵, mCPBA by Ma and co-workers¹⁶, DDQ/AcOH (Ref. 17) the reactions with **1a** did not proceed or were very sluggish.

Due to acid-sensitivity of **1a** which led to ring opening reactions and it was decided to pursue the two-step approach-benzylic bromination followed by oxidation. The N-bromosuccinimide (NBS) benzylic bromination is a standard and reliable reaction that has been used for a long time^{18–20}. However, when it was applied for the first time and for longer reaction times **1a** underwent rearrangement. It is known that during the NBS bromination small amount of HBr is liberated²¹ and in this particular case is enough to cause rearrangement of **1a**. The solution of this problem was to

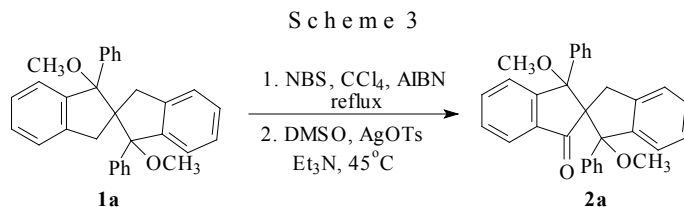
reflux the reaction mixture for maximum of 4 h and then subjected it to an aqueous and sodium bicarbonate wash. In such a way the rearrangement was minimum and 70% conversion to the desired monobromo derivative was reached. It was decided not to purify the monobromo product, because it was found to be unstable to silica gel column chromatography and the crude reaction mixture was used directly in the next (oxidation) step.

There are many methods for oxidation of the corresponding organic halides to the corresponding carbonyl compounds. The classical methods are the Hass-Bender reaction²², Sommelet reaction^{23,24}, Krohnke reaction²⁵, and Kornblum reaction^{26–28}. There are also other methods for this transformation using the following key reagents: amine N-oxides^{29–32}, pyridine N-oxide^{33,34} and related derivatives³⁵, IBX (Ref. 36), selenium compounds³⁷, NaIO₄/DMF (Ref. 38) and H₂O₂/ethanol³⁹.

Taking into consideration the nature of the substrate it was decided to use the assisted Kornblum reaction. Usually, the organic halide (bromide) is heated in DMSO in presence of base. This was not suitable in this case because it was found that **1a** is thermally unstable when heated for prolonged time above 100°C. Initially, the procedure developed by Godfrey and Ganem utilising trimethylamine N-oxide in DMSO was employed³², and it was determined that heating up to 100°C was required to accomplish the desired transformation. Since the synthetic intermediate is secondary benzylic bromide, the S_N2 reaction (displacement of bromide ion) is somewhat slower. To promote this displacement and to facilitate the reaction, it was decided to go for the silver-assisted variants^{40–42}. Once the oxysulphonium salt is formed, it undergoes fragmentation either thermally or in presence of base (Scheme 2).



The milder variants of this reaction involve non-nucleophilic silver-salts. Several procedures were taken into consideration: AgBF₄/DMSO/NEt₃ (Ref. 40) by Ganem and Boeckman, Ag₂CO₃ by Lavalee et al.⁴¹, and AgOTs/Et₃N by Wilcox et al.⁴² The desired product was first obtained by the procedure of Lavalee et al.⁴¹ albeit in very low yield (10%). It was speculated that the prolonged heating of the monobromobenzylic derivative of **1a** caused rearrangement and effectively decreased the yield. The procedure by Wilcox et al.⁴² had been carried out at the lowest reaction temperature (45°C) and was the next logical choice.



By utilising the two-step sequence, NBS benzylic bromination, silver-assisted Kornblum type oxidation with AgOTs/Et₃N, the desired **2a** was obtained in 28% overall yield (Scheme 3). It is important to note that the DMSO used in the last step must be anhydrous, in order to avoid hydrolysis of the bromide, which effectively decreases the yield of the desired **2a**.

CONCLUSIONS

The 1,1'-diaryl-2,2'-spirobiindane derivatives and indane, as a model compound, were treated with various oxidising agents in order to achieve selective benzylic oxo-functionalisation. Even though, the model compound, indane, was successfully converted to 1-indanone, using several literature procedures, when they were used on the 1,1'-dimethoxy-1,1'-diphenyl-2,2'-spirobiindane derivatives, they either failed or complex mixture of products was obtained. The reactant, **1a**, is thermally and acid-sensitive, and undergoes ring-opening reactions. This severely limited the choice of oxidants and direct benzylic oxo-functionalisation was not successful. The benzylic oxo-functionalisation was achieved on the 1,1'-dimethoxy derivative in two steps using NBS benzylic bromination followed by silver-assisted Kornblum type oxidation.

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REFERENCES

1. M. HUDLICKY: Oxidations in Organic Chemistry. American Chemical Society, Washington, D. C., 1990.
2. D. H. B. RIPIN: Oxidations. In: Practical Synthetic Organic Chemistry: Reactions, Principles and Techniques (Ed. S. Caron). Vol. 10. John Wiley & Sons, Inc., Hoboken, New Jersey, 2011, 493–556.
3. G. CAINELLI, G. CARDILLO: Chromium Oxidations in Organic Chemistry. Springer, Berlin, 1984.
4. R. A. SHELDON, J. K. KOCHI: Metal-catalyzed Oxidations of Organic Compounds. Academic Press, New York, 1981.
5. V. V. ZHDANKIN: Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds. John Wiley & Sons, New York, 2013.
6. R. W. MURRAY, R. JEYARAMAN: Dioxiranes: Synthesis and Reactions of Methyl dioxiranes. *J Org Chem*, **50**, 2847 (1985).
7. R. W. MURRAY: Chemistry of Dioxiranes. 12. Dioxiranes. *Chem Rev*, **89**, 1187 (1989).

8. X. L. TONG, J. XU, H. MIAO, J. GAO: New Efficient Organocatalytic Oxidation of Benzylic Compounds by Molecular Oxygen under Mild Conditions. *Tetrahedron Lett*, **47**, 1763 (2006).
9. J. BOGDANOV: Electron Delocalization in Spiroconjugated Systems. Ph. D. Thesis, The Pennsylvania State University, 2005.
10. W. C. STILL, M. KAHN, A. MITRA: Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J Org Chem*, **43**, 2923 (1978).
11. W. M. HARMS, E. J. EISENBRAUN: Chromic Acid Oxidation of Indanes and Hydrindacenes. Synthesis of 1,1-dimethylindene. *Org Prep Proced Int*, **4**, 67 (1972).
12. R. P. JACOBSEN: The Preparation and Properties of Dehydroabietophenone (Nordehydroabietyl Phenyl Ketone) and 6-hydroxydehydroabietophenone. *J Am Chem Soc*, **73**, 3463 (1951).
13. R. RATHORE, N. SAXENA, S. CHANDRASEKARAN: A Convenient Method of Benzylic Oxidation with Pyridinium Chlorochromate. *Synth Commun*, **16**, 1493 (1986).
14. K. C. NICOLAOU, T. MONTAGNON, P. S. BARAN, Y. L. ZHONG: Iodine(V) Reagents in Organic Synthesis. Part 4. *o*-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-based Oxidation Processes. *J Am Chem Soc*, **124**, 2245 (2002).
15. D. KUCK, A. SCHUSTER: Oxidations of Alkylbenzenes with Dimethyldioxirane. *Z Naturforsch B*, **46**, 1223 (1991).
16. D. MA, C. XIA, H. TIAN: Oxidation of Benzylic Methylene Compounds to Ketones with *m*-Chloroperoxybenzoic Acid and Oxygen. *Tetrahedron Lett*, **40**, 8915 (1999).
17. H. LEE, R. G. HARVEY: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in Acetic Acid, a Convenient New Reagent for the Synthesis of Aryl Ketones and Aldehydes via Benzylic Oxidation. *J Org Chem*, **53**, 4587 (1988).
18. A. WOHL: Bromierung Ungesättigter Verbindungen Mit N-Brom-Acetamid, Ein Beitrag Zur Lehre Vom Verlauf Chemischer Vorgänge. *Berichte der Deutschen Chemischen Gesellschaft (A and B Series)*, **52**, 51 (1919).
19. K. ZIEGLER, G. SCHENCK, E. W. KROCKOW, A. SIEBERT, A. WENZ, H. WEBER: Die Synthese Des Cantharidins. *Justus Liebigs Ann Chem*, **551**, 1 (1942).
20. C. DJERASSI: Brominations with N-bromosuccinimide and Related Compounds. The Wohl-Ziegler Reaction. *Chem Rev*, **43**, 271 (1948).
21. J. H. INCREMONA, J. C. MARTIN: N-bromosuccinimide. Mechanisms of Allylic Bromination and Related Reactions. *J Am Chem Soc*, **92**, 627 (1970).
22. H. B. HASS, M. L. BENDER: The Reaction of Benzyl Halides with the Sodium Salt of 2-nitropropane. A General Synthesis of Substituted Benzaldehydes. *J Am Chem Soc*, **71**, 1767 (1949).
23. M. SOMMELET: Sur Un Mode De Décomposition Des Halogénoalcoylates D'hexaméthylène – Tétramine. *Comp Rend Acad Sci*, **157**, 852 (1913).
24. S. J. ANGYAL, P. J. MORRIS, J. R. TETAZ, J. G. WILSON: The Sommelet Reaction. Part III. The Choice of Solvent and the Effect of Substituents. *J Chem Soc*, 2141 (1950).
25. F. KRÖHNKE: Syntheses Using Pyridinium Salts (IV). *Angew Chem, Int Ed. Engl.*, **2**, 380 (1963).
26. N. KORNBLUM, J. W. POWERS, G. J. ANDERSON, W. J. JONES, H. O. LARSON, O. LEVAND, W. M. WEAVER: A New and Selective Method of Oxidation. *J Am Chem Soc*, **79**, 6562 (1957).
27. N. KORNBLUM, W. J. JONES, G. J. ANDERSON: A New and Selective Method of Oxidation. The Conversion of Alkyl Halides and Alkyl Tosylates to Aldehydes. *J Am Chem Soc*, **81**, 4113 (1959).
28. N. KORNBLUM, H. W. FRAZIER: A New and Convenient Synthesis of Glyoxals, Glyoxalate Esters, and Alpha-Diketones. *J Am Chem Soc*, **88**, 865 (1966).
29. V. FRANZEN: Octanal. *Org Synth*, **5**, 872 (1973).
30. S. SUZUKI, T. ONISHI, Y. FUJITA, H. MISAWA, J. OTERA: A Convenient Method for Conversion of Allylic Chlorides to Alpha, Beta-unsaturated Aldehydes. *Bull Chem Soc Jpn*, **59**, 3287 (1986).
31. S. CHANDRASEKHAR, M. SRIDHAR: A Bifunctional Approach Towards the Mild Oxidation of Organic Halides: 2-dimethylamino-N,N-dimethylaniline N-oxide. *Tetrahedron Lett*, **41**, 5423 (2000).

32. A. G. GODFREY, B. GANEM: Ready Oxidation of Halides to Aldehydes Using Trimethylamine N-oxide in Dimethylsulfoxide. *Tetrahedron Lett*, **31**, 4825 (1990).
33. D. BARBRY, P. CHAMPAGNE: Fast Synthesis of Aromatic Aldehydes from Benzylic Bromides without Solvent under Microwave Irradiation. *Tetrahedron Lett*, **37**, 7725 (1996).
34. D. X. CHEN, C. M. HO, Q. Y. RUDY WU, P. R. WU, F. M. WONG, W. WU: Convenient Oxidation of Benzylic and Allylic Halides to Aldehydes and Ketones. *Tetrahedron Lett*, **49**, 4147 (2008).
35. S. MUKAIYAMA, J. INANAGA, M. YAMAGUCHI: 4-Dimethylaminopyridine N-oxide as an Efficient Oxidizing Agent for Alkyl Halides. *Bull Chem Soc Jpn*, **54**, (1981).
36. J. N. MOORTHY, N. SINGHAL, K. SENAPATI: Oxidations with IBX: Benzyl Halides to Carbonyl Compounds, and the One-pot Conversion of Olefins to 1,2-diketones. *Tetrahedron Lett*, **47**, 1757 (2006).
37. L. SYPER, J. MLOCHOWSKI: A Convenient Oxidation of Halomethylarenes and Alcohols to Aldehydes with Dimethyl Selenoxide and Potassium Benzeneselenite. *Synthesis*, **9**, 747 (1984).
38. S. DAS, A. K. PANIGRAHI, G. C. MAIKAP: NaIO₄-DMF: A Novel Reagent for the Oxidation of Organic Halides to Carbonyl Compounds. *Tetrahedron Lett*, **44**, 1375 (2003).
39. J. TANG, J. ZHU, Z. SHEN, Y. ZHANG: Efficient and Convenient Oxidation of Organic Halides to Carbonyl Compounds by H₂O₂ in Ethanol. *Tetrahedron Lett*, **48**, 1919 (2007).
40. B. GANEM, R. K. BOECKMAN JR: Silver-sssisted Dimethylsulfoxide Oxidations; an Improved Synthesis of Aldehydes and Ketones. *Tetrahedron Lett*, **15**, 917 (1974).
41. J.-F. LAVALLEE, R. REJ, M. COURCHESNE, D. NGUYEN, G. ATTARDO: Synthesis of a 5-deoxypranoanthracycline: An Entry into Novel Analogs of Idarubicin. *Tetrahedron Lett*, **34**, 3519 (1993).
42. C. F. WILCOX, K. R. LASSILA, G. VANDUYNE, H. LU, J. CLARDY: Synthesis and Properties of Cycloocta[def]Biphenylene-1,4-dione. *J Org Chem*, **54**, 2190 (1989).

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